ASYMMETRIC INDUCTION IN 1,3-DIPOLAR CYCLOADDITION USING CHIRAL NITRONES

BY

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A Dissertation Presented to the

DEANSHIP OF GRADUATE STUDIES

KING FAHD UNIVERSITY OF PETROLEUM & MINERALS

DHAHRAN, SAUDI ARABIA

In Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY

In

CHEMISTRY

MAY 2010

KING FAHD UNIVERSITY OF PETROLEUM & MINERALS

DHAHRAN 3126, SAUDI ARABIA

DEANSHIP OF GRADUATE STUDIES

This dissertation, written by BASEM A. MOOSA under the direction of his advisor and approved by his thesis committee, has been presented to and accepted by the Dean of Graduate Studies, in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY in CHEMISTRY.

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ABSTRACT

NAME: Basem Abdel Hamid Moosa

TITLE: Asymmetric Induction In 1,3-Dipolar Cycloaddition Using Chiral Nitrones

MAJOR: Chemistry

DATE: 2010

This thesis describes the development of methods for the preparation of chiral racemic substituted cyclic and a cyclic nitrones. This has been accomplished by the following points.

In chapter 3, the diastereoselectivity in the cycloaddition reactions of several mono- and disubstituted alkenes with a (-)norephedrine-derived methylenenitrone has been investigated. The stereochemical analysis of the addition products (i.e. isoxazolidines) has been carried out by X-ray, NMR and chemical conversions. The NMR spectra of the isoxazolidines at low temperatures indicated the presence of either a single or a predominant invertomer. The stereochemistry of the invertomers and nitrogen inversion barriers are determined using complete line-shape analysis and their dependence on solvent is discussed.

In chapter 4, a study of the stereo- and face-selectivity of the cycloaddition reactions of several mono- and disubstituted alkenes with 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide has been carried out. The addition reactions have displayed a very high degree of face selectivity (13-48:1). Use of dimethyl methylenemalonate as a protective group in nitrone cycloaddition reactions has been demonstrated. The invertomeric analysis revealed that the bicyclic cycloadducts remain predominantly as the cis-fused isomer which leads to the formation of synthetically important second-generation cyclic aldonitrones via peracid oxidation. One interesting finding was that treatment of the cycloadducts with two equivalents of peracid afforded the cyclic N-hydroxy lactams, presumably via further oxidation of the aldonitrones. The piperidine ring has been elaborated by cycloaddition reaction of the second-generation nitrones with several alkenes, which in most cases gave the cycloadducts in a stereoselective manner.

In chapter 5, the cycloaddition reactions of 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide with mono- and di-substituted alkenes have been found to be

highly stereo- as well as face-selective. In solution, the 6/5 fused bicyclic cycloadducts remain solely as the cis-fused invertomers in order to accommodate the bulky tertiary substituent 2-hydroxy-2-propyl in the equatorial orientation. The cycloadducts, upon peracid oxidation, leads to the exclusive formation of synthetically important second-generation cyclic aldonitrones. The stereo- and face-selectivity of the cycloaddition reactions of these second-generation nitrones bearing substituents at C(4) and C(6) have been briefly examined.

In chapter 6, One interesting finding was that treatment of the first generation nitrone i.e., 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide or 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide, with mercury(II) oxide afforded novel bicyclic nitrones, 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxides, whose cycloaddition reactions were briefly examined.

In chapter 7, the cycloaddition reaction of 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide with butyl vinyl ether was used as a key step in the short stereoselcetive racemic synthesis of ladybird beetle alkaloid 2-epicalvine. The cycloadduct on quartenization with 2-bromoethanol followed by ring openinng and lactonization afforded the natural product in a single pot reaction.

Doctor of Philosophy
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May , 2010

الإسم: **باسم عبد الحميد موسى**

عنوان الرسالة : الحث غير المتجانس لتفاعلات الإضافة الحلقية 1,3 ثنائية القطب باستخدام نيترونات يدوية

التخصص: الكيمياء

التاريخ:2010

هذه الدراسة تصف عدة طرق لتحضير مركبات الجيل الثاني من الألدونيترونات الحلقية اليدوية (Chiral) ذات المزيج الراسيمي (Racemic) بواسطة الفوق أسيد (Peracid) تم ذلك عن طريق ما يلي :
1-دراسة الانتقاء الفراغي للعديد من تفاعلات الاضافة الحلقية لمجموعة من المركبات أحادية و ثنائية الألكينات بواسطة النيترون الميثيلي مشتق النورفيدين . تم أيضا " تحليل السلوك الكيميائي الانتقائي الفراغي (Stereochemical Analysis) عند اضافة الأيزوكسزولدينات بواسطة الرنين النووي المغناطيسي (NMR) (البلورة الأحادية) والأشعة السينية (X-Ray) والتحولات الكيميائية (Chemical Conversions) .
2- دراسة الانتقائية الوجهية و الانتقائية الفراغية لتفاعلات الاضافة الحلقية للعديد من الألكينات الأحادية و الثنائية مع 4-هيدروكسي ميثيل- 3, 6,5,4 -رباعي هيدرو بيريدين 1-أوكسايد .أظهرت تفاعلات الاضافة درجة عالية من الانتقائية الوجهية (13-48: 1). كشف التحليل العكسي أن المركبات ثنائية الحلقية تبقى بشكل دائم على هيئة السس آيزومر (*cis*- isomer) والذي يؤدي إلى تكوين ألدونيترونات الجيل الثاني ذات الأهمية الكبيرة تصنيعيا " بواسطة أكسدة فوق الأسيد (Peracid). من النتائج المثيرة للاهتمام لوحظ أنه عند معاملة المركبات الحلقية بكميتين متساويتين من الفوق الأسيد تم تعزيز انتاج (ن)-هيدروكسي لا كتمات الحلقية.و الذي يفسر بواسطة الأكسدة الاضافية للألدونيترونات.
3- دراسة تفاعلات الاضافة الحلقية لمركب 4-(2-هيدروكسي-2-بروبيل)-6,5,4,3-رباعي هيدرو ببريدين 1-أوكسايد مع ألكينات ثنائية و أحادية . كانت النتائج مركبات عالية الانتقائية الوجهية و الانتقائية الفراغية. بمحلول 6/5 المركبات ثنائية الحلقية بقيت على هيئة السس (*cis*-fused invertomers) لمواجهة الازدحام الناجم عن المركب المتفرغ الثلاثي (tertiary substituent) (2-هيدروكسي - 2- بروبيل) في الفضاء الاستوائي (equatorial orientation). كنتيجة للأكسدة فوق أسيد فإن المركبات الحلقية كونت المزيد من مركبات الجيل الثاني من الألدونيترونات الحلقية والتي لها أهمية تصنيعية عظيمة . كما أن الانتقائية الوجهية و الانتقائية الفضائية في تفاعلات الاضافة الحلقية لألدونيترونات الجيل الثاني الناتجة تحمل مجموعات على كربونة رقم (4) كربونة رقم (6) و التي تم فحصها باختصار.
4-دراسة الانتقائية الوجهية و الانتقائية الفرغية لتفاعلات الاضافة الحلقية له ذا النوع الجديد من النيترونات ثنائيةالحلقية. ثم دراسة العلاقة ما بين الكيمياء الفراغية في تفاعلات الاضافة للنيترونات ثنائية الحلقية (209 و 210) و النيترونات أحادية الحلقية (140 و192).
5- كتطبيق عملي دو أهمية لهده الدراسة تم تصنيع ولأول مرة 2-إبيكالفن (2-epicalvine) و الدي يعتبر منتج قلوي طبيعي باستخدام تفاعلات الاضافة الحلقية ثنائية القطبية (DC) وهدا يوضح مدى الأهمية التصنيعية لهدا النوع من النيترونات الحلقية التي تستخدم كمواد أولية لتحضير منتجات طبيعية.

درجة الدكتوراة في الفلسفة
جامعة الملك فهد للبترول والمعادن
الظهران، المملكة العربية السعودية
2010 م

ABBREVIATION

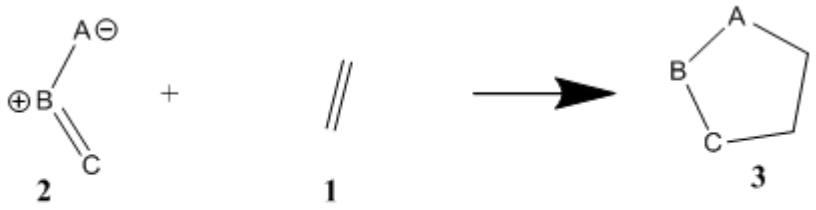
$[\alpha]_D$	Specific rotation at λ = 599.6 nm
Ac	Acetyl
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bp	Boiling point
CI	Chair Inversion
CM	Cross Metathesis
CN(R,S)	Chiral *N*cyanomethyloxazolidine
DC	dipolar cycloaddition
DEPT	Distortionless Enhancement by Polarization Transfer
DMAP	Dimethyl AminoPyridine
DMD	Dimethyldioxirane
DMSO	Dimethylsulfoxide
HOMO	Highest Occupied Molecular Orbital
IR	Infrared
LDA	Lithium DiisopropylAmide
LUMO	Lowest Unoccupied Molecular Orbital
MS	Mass spectrometry
m.p	Melting point
m/z	Mass- to- charge ratio
MCPBA	m-Chloroperbenzoic Acid
NBS	N-Bromosuccinimide
NI	Nitrogen Inversion
NMR	Nuclear Magnetic Resonance

Ph	Phenyl
ppm	Part per million
p-tosic acid	p-toluene sulfonic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
tRNA	Transfer Ribonucleic Acid
$\Delta G^{\#}$	Free energy of activation
δ	Chemical Shift

CHAPTER 1

1.1 Introduction

The 1,3-dipolar cycloaddition (DC) is a reaction where two organic compounds, a dipolarophile, **1**, and a 1,3-dipole (or ylide), **2**, combine to form a five membered heterocycle **3** (Scheme 1). The reaction is related to Diels- Alder reaction where a diene and a dienophile form a six membered ring. From simple starting materials, the 1,3-dipolar cycloaddition reaction can furnish very complex heterocycles, containing multiple stereogenic centers. Therefore, this reaction is often used as a key step in the syntheses of many natural products and pharmaceuticals. After its discovery in 1888, with diazoacetic ester as the 1,3- dipole, various other 1,3-dipoles have been used in this type of reaction. [1, 2].

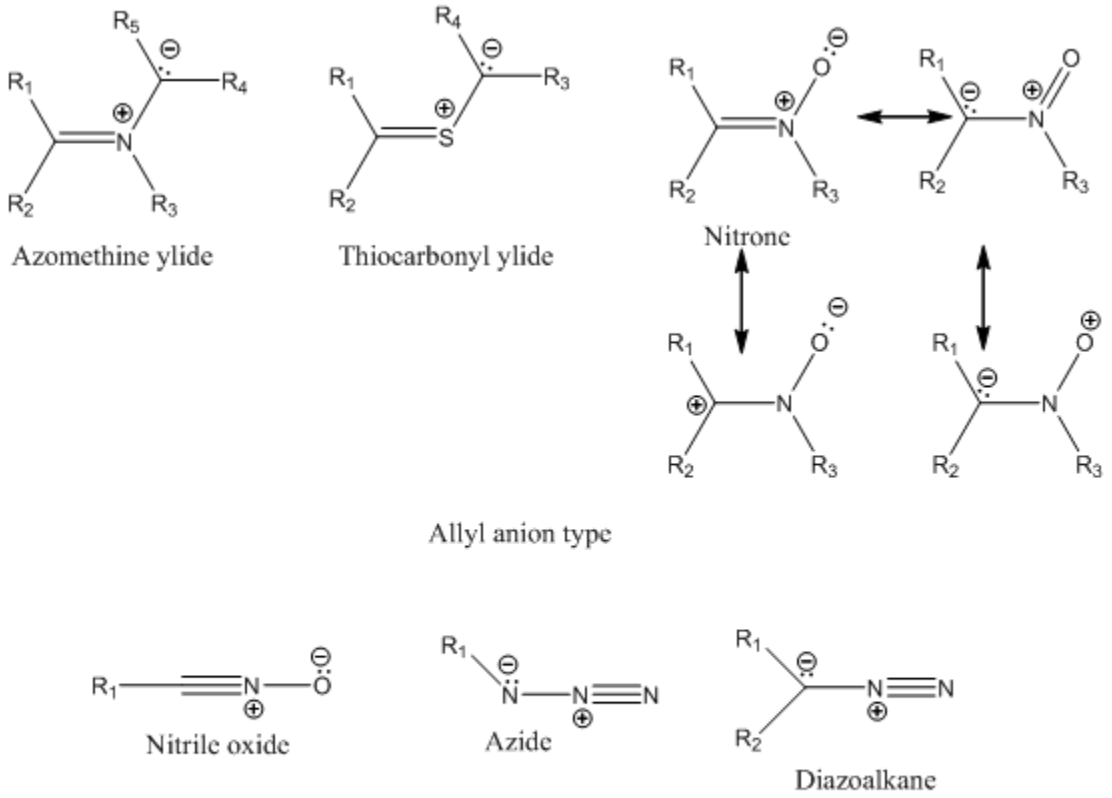


2 **1** **3**

Scheme 1.

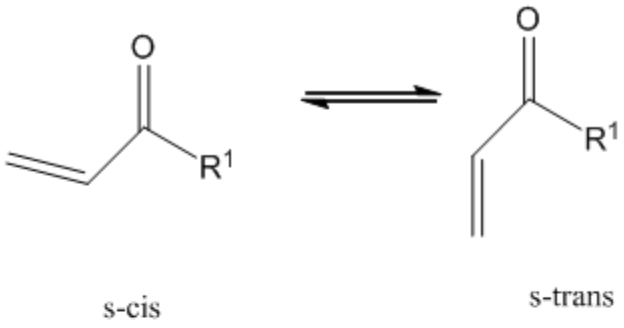
The 1,3-dipole, also known as an ylide, bears a positive and a negative charge distributed over three atoms and has 4π electrons. The most common atoms incorporated in the 1,3-dipole are nitrogen, carbon, oxygen or sulfur. Representative examples of some 1,3-dipoles are shown in (Scheme 2) [2], These are devided into two groups; the allyl anion type which has a bent structure and the propargyl/allenyl anion type with a linear structure . Each of these dipoles has four resonance structures as exemplified for the nitrone. The ylide can, depending on the nature of the 1,3-dipole, exist in an equilibrium

between an *E*-form and a *Z*-form. This can have consequences for the diastereoselectivity in reactions with dipolarophiles



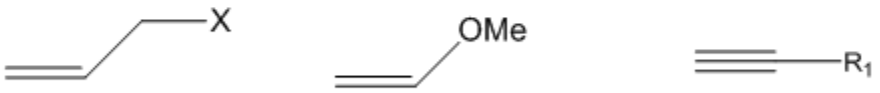
Scheme 2.

The dipolarophile in a 1,3-dipolar cycloaddition is a reactive alkene moiety containing 2π electrons. Like, α,β- unsaturated aldehydes, ketones, and esters, allylic alcohols, allylic halides, vinylic ethers and alkynes are examples of dipolarophiles that react readily (Scheme 3). It must be noted, however, that other 2π- moieties such as carbonyls and imines also can undergo cycloaddition with dipoles. The alkene moiety can be mono-, di-, tri- or even tetrasubstituted (only monosubstituted ones are shown here). However, mostly due to steric factors, tri- and tetrasubstituted ones often display very low reactivity in reactions with dipoles [3].



s-cis s-trans

R^1 = H, Me or OMe



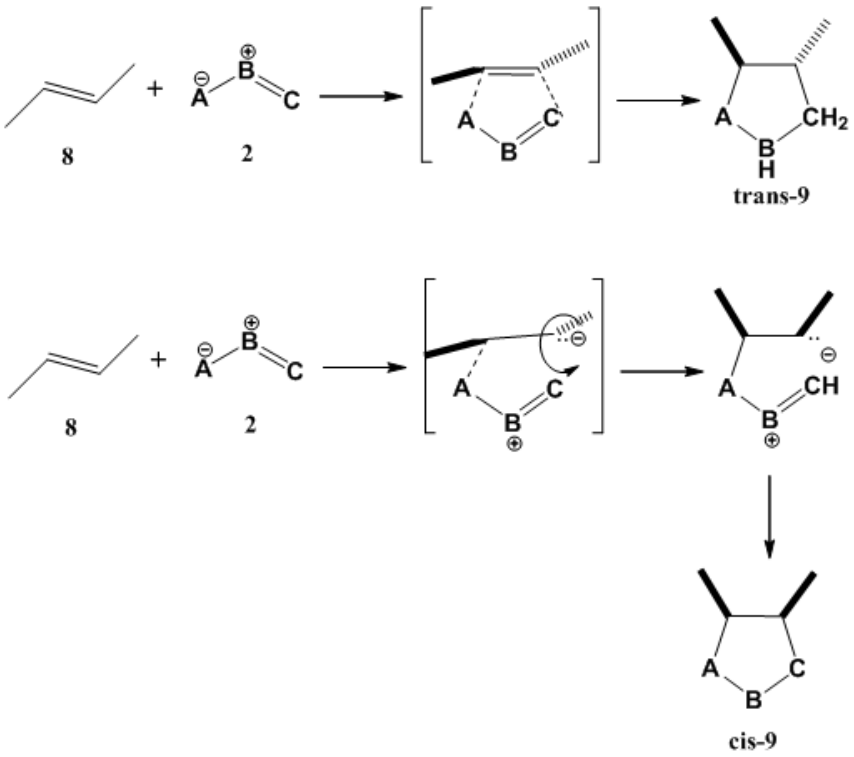
X = OH or halogen

Scheme 3.

1.2 Mechanism of DC

The 1,3-dipolar cycloaddition reaction of a 1,3-dipole with a dipolarophiles involves an interaction between the 4π electrons of the dipole/ylide and the 2π electrons of the dipolarophiles. The reaction mostly proceeds in a concerted manner, which means that all bonds are created simultaneously, but not necessarily to the same extent at a certain time. Consequently, the stereochemistry of the dipolarophile is conserved in the final product. This is exemplified in (Scheme 4), where *trans*-2-butene (**8**) reacts with the hypothetical dipole furnishing exclusively *trans*-product. Starting from the *cis* isomer of butene **(8)** will thus yield the *cis* isomer product [4].

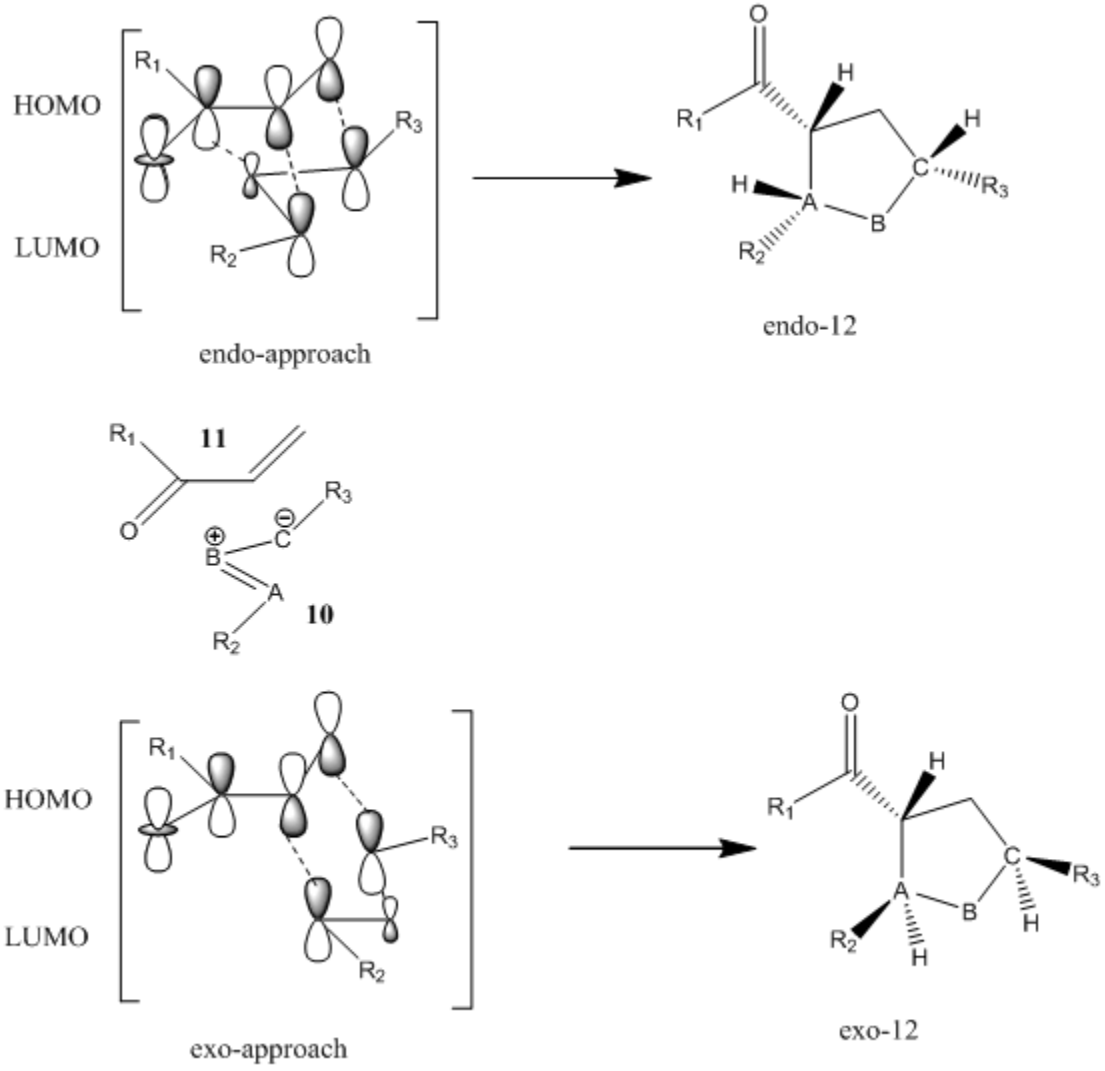
If, on the other hand, the reaction proceeds *via* a two-step mechanism, the stereochemistry of the starting dipolarophile is not necessarily conserved throughout the whole reaction. This is exemplified in (Scheme 4**)**, where *trans*-2- butene (**8**) reacts with the dipole in a two-step fashion furnishing the diastereomer *cis*-**9** *via* isomerisation of the starting dipolarophile.



Scheme 4

Depending on the nature of the dipole and the dipolarophile, the 1,3-dipolar cycloaddition reaction is controlled either by a LUMO (dipolarophile)- HOMO (dipole)- or a LUMO (dipole)-HOMO (dipolarophile) interaction but in some cases a combination of both interactions is involved. An example of a LUMO (dipolarophile)-HOMO (dipole) controlled reaction is depicted in Scheme 5. The approach of the dipole (e.g. **10**) to the dipolarophile (e.g. **11**) can occur in an *endo* or *exo* mode resulting in two diastereomeric

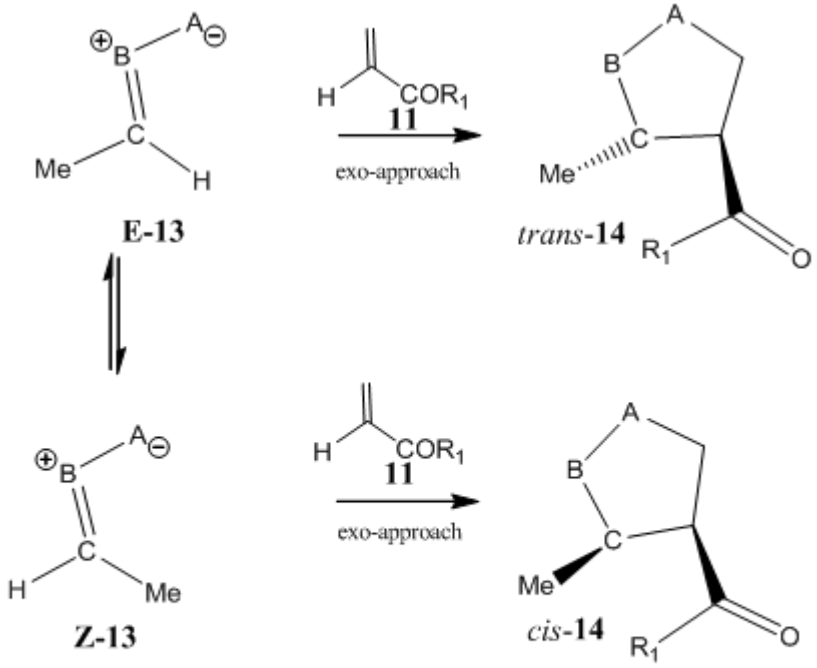
endo/*exo* cycloadducts, *endo*-**12** and *exo*-**12**, respectively. An overview over both these approaches is depicted in (Scheme 5) where the *endo* approach is stabilised by small secondary π-orbital interactions, contributing to the *endo*/*exo* selectivity of the reaction [5].



Scheme 5

However, other factors such as steric ones can have a major influence on this *endo*/*exo* selectivity and can often override this stabilizing effect. Moreover, depending on the substitution pattern of the ylide, this can exist in equilibrium between a *Z*-form and an

E-form. Reaction of each of these isomers with a dipolarophile, gives rise to diastereomeric cycloadducts, provided that the approach of these (*endo* or *exo*) is the same. This is exemplified in Scheme **6** where ylides *E*-**13** and *Z*-**13** react with the dipolarophile **11** *via* an *exo*-approach furnishing diastereomeric cycloadducts *trans*-**14** and *cis*-**14** respectively. The *cis*/*trans* nomenclature for the description of the stereochemistry of the cycloadducts is thus often used instead of the *exo*/*endo* one to avoid confusion when ylides existing as an equilibrating mixture of *Z*/*E* isomers are used [6-10].



Scheme 6.

1.3 Nitrones

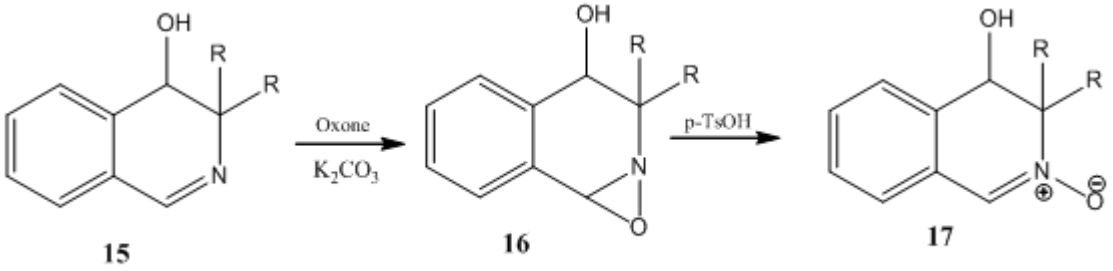
1,3-Dipolar cycloaddition reactions offer one of the most versatile synthetic routes to five-membered heterocycles, and the reactions of nitrone dipoles play an important part

in the history of cycloaddition reactions. These particular dipolar cycloaddition reactions can be considered as concerted but asynchronous [4π – 2π] suprafacial processes and the reactions allow creation of up to three contiguous carbon stereocentres in a single step. In any nitrone–alkene cycloaddition reaction, two pairs of regioisomeric and diastereoisomeric products can result and these arise from the nitrone and alkene approaching each other in either of two regiochemical senses, and in either an *endo*- or an *exo*-fashion Scheme 5. Therefore, much effort has focussed on the development of regioselective and stereoselective nitrone–alkene cycloaddition reactions [9-11]. Nitrones have been used in numerous studies of asymmetric 1,3-dipolar cycloadditions. In general, nitrones are relatively stable species and do not need to be prepared *in situ*. Nitrones could be generated or prepared by two main methods (Oxidative and non-oxidative methods).

1.3.1. Oxidative Methods

1.3.1.1 Oxidation of imines

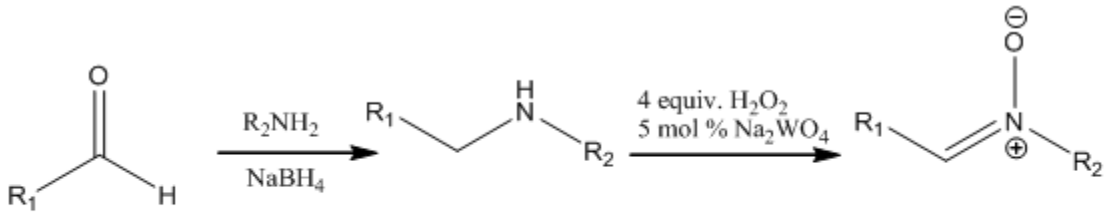
Oxidation of imines leads to oxaziridines which can be rearranged to nitrones. Different types of oxidant could be used in this type of reaction such as MCPBA (m-chloroperbenzoic acid), Oxone (potassiumperoxymonosulfate), DMD (dimethyldioxirane), methyl (trifluoromethyl) dioxirane and peroxides like hydrogen peroxide and tert-butylhydroperoxide. Oxidation of 3,4-dihydroisoquinoline (**15**) with Oxone initially leads to the formation of oxaziridine (**16**) which is easily transformed into the corresponding 3,4 dihydroisoquinoline N-oxide (**17**) upon treatment with catalytic amounts of p-toluenesulfonic acid (Scheme 7) [20-24].



Scheme 7.

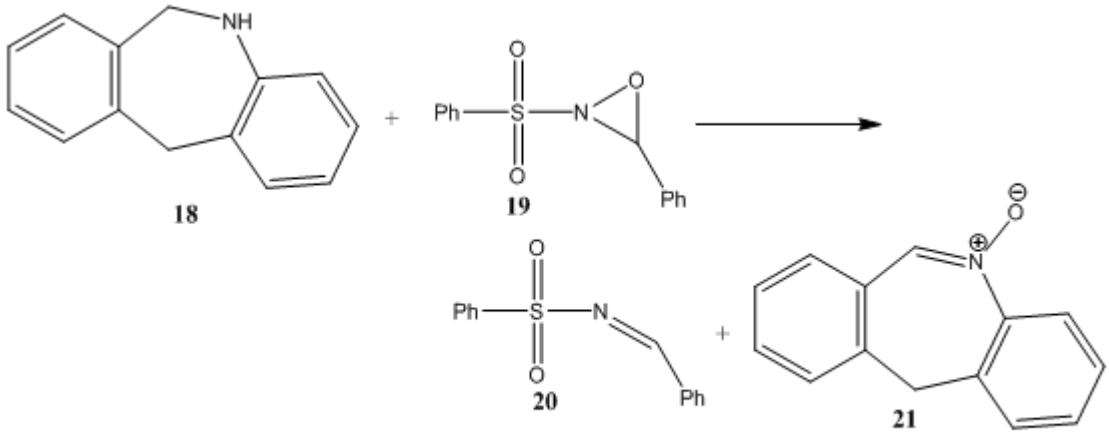
1.3.1.2 Oxidation of amines

Oxidation of secondary amines into nitrones has been extensively studied and a variety of well-known efficient oxidants and catalysts which can be employed in this process are available. Catalytic oxidation by hydrogen peroxide at room temperature is carried out by using sodium tungstate (Scheme 8).



Scheme 8.

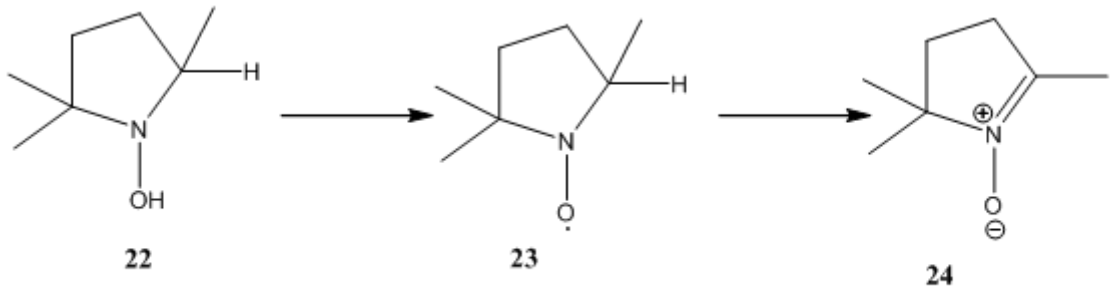
C-Phenyl-N-phenylsulfonyloxaziridine (**19**) (Davis reagent) is also used as an oxaziridine type oxidant. The use of this reagent in oxidation of diazepine (**18**), give the corresponding nitrones (**21**) in quantitative yields (Scheme 9) [25-32].



Scheme 9.

1.3.1.3 Oxidation of hydroxylamines

The mildest oxidation method of nitrone formation seems to be *via* oxidation of the corresponding hydroxylamines (**22**) containing one or more protons at α-C. In this reaction, air, H_2O_2, MCPBA, oxides of different metals (MnO_2, PbO_2, HgO, Ni_2O_3, etc.) can be used as oxidants. The resulting nitroxyl radicals (**23**) undergo a disproportionation reaction (Scheme 10), and with an excess of the oxidant, give nitrones (**24**) as the reaction products [33,34].



22 23 24

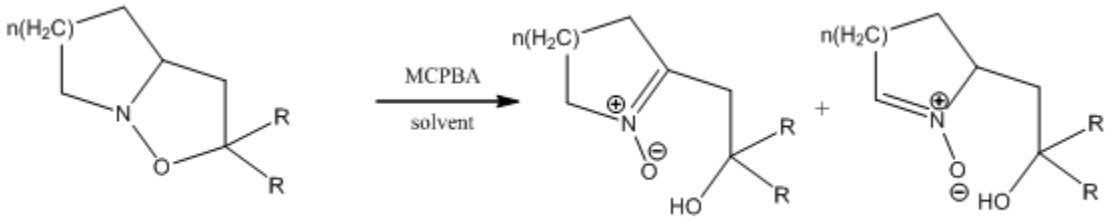
Scheme 10.

In a mechanistic study of oxidation of N-benzyl-N-alkyl hydroxylamines, with HgO and p-benzoquinone, it has been proposed on the basis of intra- and intermolecular

kinetic isotope effects that, initially, there takes place a one-electron transfer from a nitrogen atom to the oxidant, with a subsequent proton abstraction. Oxidation of cyclic and acyclic hydroxylamines with yellow mercuric oxide appears to proceed with high regioselectivity. Regioselectivity is determined by the electronic nature of the substituents. The oxidative regioselectivity of MnO_2 is comparable to that of HgO, but due to its lower toxicity, it has been proposed to use MnO_2 rather than HgO.

1.3.1.4 Oxidation of bicyclic isoxazolidines

Oxidative ring opening of isoxazolidines leads to nitrones. Thus, bicyclic isoxazolidines (**25**) and (**26**), treated with MCPBA, afford nitrones (**27**), (**28**), (**29**), and (**30**) (Scheme 11). Conformational analysis has confirmed the key role of the nitrogen lone pair with respect to regioselectivity of the reaction and of the intramolecular kinetic deprotonation of the intermediate oxoammonium derivative. Similar oxidative ring opening occurs in other bi- and tricyclic isoxazolidines upon treatment with MCPBA [35,36].



n = 1 **25**
n = 2 **26**

27 : 29
27 : 29
28 : 30

27
28

0:100 in CH_2Cl_2
100:0 in CH_3CO_2H
85: 15 inCH_2Cl_2

29
30

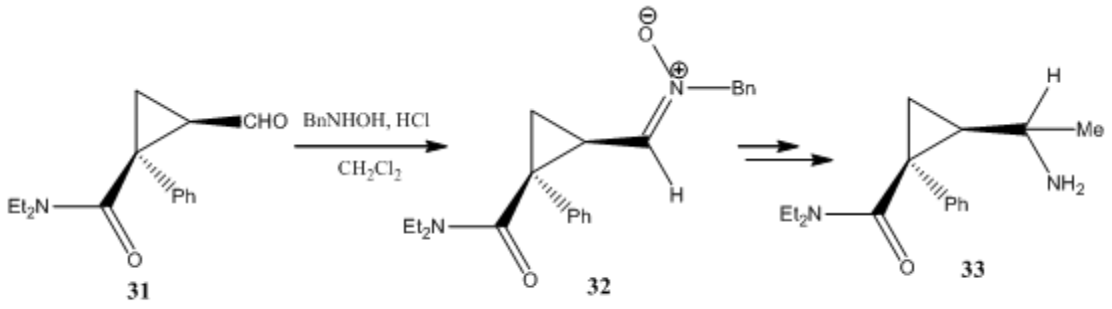
Scheme 11.

1.3.2 Non-Oxidative Methods

1.3.2.1 Condensation of secondary hydroxylamines with carbonyl compounds

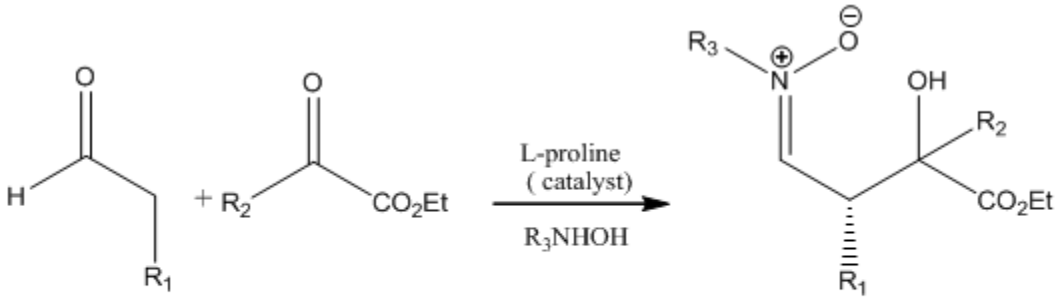
Condensation of N-monosubstituted hydroxylamines with carbonyl compounds is used as a direct synthesis of many acyclic nitrones. The condensation is carried out under mild conditions; this allows the synthesis of various nitrones to proceed without affecting functional groups. Thus, condensation of various aromatic, heteroaromatic, and aliphatic aldehydes with alkylhydroxylamines makes it possible to synthesize a variety of N-alkylnitrones [37-39].

The main building block of PEDC (**33**) (1-phenyl-2-[(S)-1-aminoethyl]-N,N -diethylcyclopropanecarboxamide), a potent NDMA (N-methyl-D-aspartic acid) receptor antagonist of a cyclopropane structure, N-benzyl-C-cyclopropyl nitrone(**32**) was generated in quantitative yield by condensation of asymmetric cyclopropylcarbaldehyde (31) with N-benzylhydroxylamine hydrochloride in CH_2Cl_2 (Scheme 12) [40,41].



Scheme 12.

The synthesis of optically active nitrones (**36**) was carried out by an aldol reaction of aldehydes (**34**), catalyzed by L- proline, with carbonyl activated compounds (**35**) and by an *in situ* reaction with N-alkylhydroxylamines (Scheme 13), (Table 1) [42].



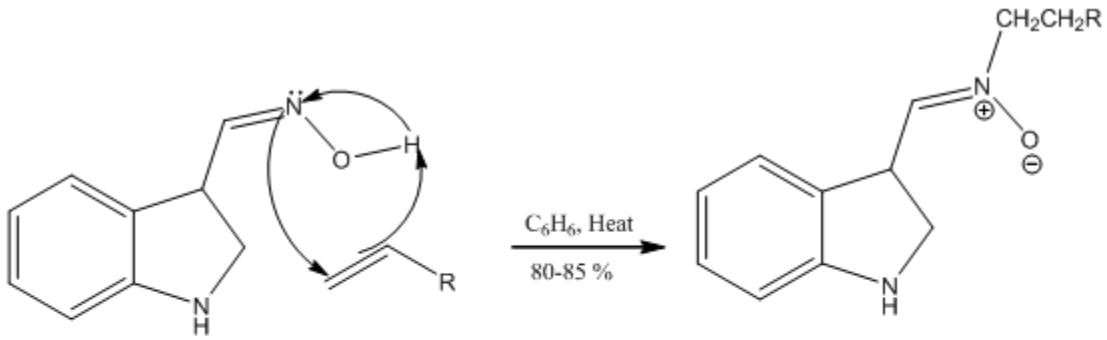
34 **35** **36**

Scheme 13.

Table 1. Formation of optically active functionalized β-hydroxy-nitrones **36** by reaction of aldehydes **34** with activated carbonyl compounds **35** and substituted N-alkyl hydroxylamine hydrochloride in the presence of L-proline as the catalyst.				
R_1	**R_2**	**R_3**	**Yield (%)**	**ee (%)**
Me	CO_2Et	Bu	95	77
Et	CO_2Et	Bu	95	92
Me	CO_2Et	Bn	95	83
Et	CO_2Et	Bn	95	92
i-Pr	CO_2Et	Bn	95	96
Allyl	CO_2Et	Bu	95	86
Me	CF_3	Bu	95	91

1.3.2.2 Synthesis from oximes

Alkylation of oximes at the nitrogen atom with various reagents seems to be one of the easiest and convenient methods for synthesizing nitrones. The significant advantage of this method is that there is no need to use oxidants. Electron poor alkenes, resulting from the activation of electron-accepting groups and action of electrophiles or metal ions as catalysts, are used as the most available alkylating agents. The reaction known as Grigg's nitrone formation, involving formal Michael addition is widely used. In most cases, the resulting nitrones quickly enter into a specific 1,3-cycloaddition reaction. Similar transformations are observed in the reactions of oximes with alkynes. Therefore, Grigg's reaction, which seems very effective in using the sequence of oxime-nitrone-products and 1,3-dipolar cycloaddition, can hardly be considered as an overall synthetic approach to nitrones [43-47]. However, under certain conditions, the resulting nitrones can be isolated. Thus, the reaction of indol-oxime (**37**) with methyl acrylate, methyl vinyl ketone, acrylonitrile, and acrylamide gives indol-nitrones (**38**) (Scheme 14).

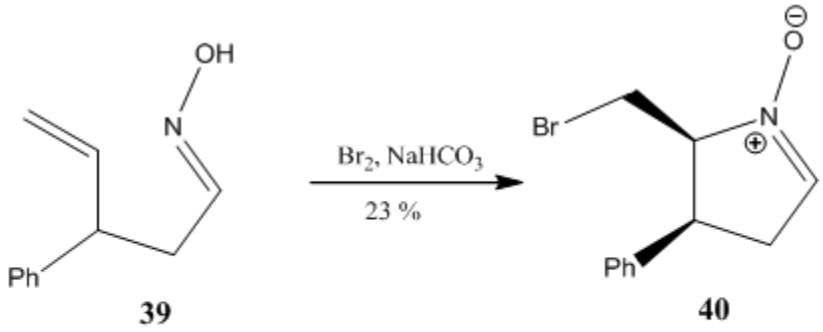


37 a-d **38 a-d**

R = a) $COOCH_3$, b) $COCH_3$, c) CN, d) $CONH_2$

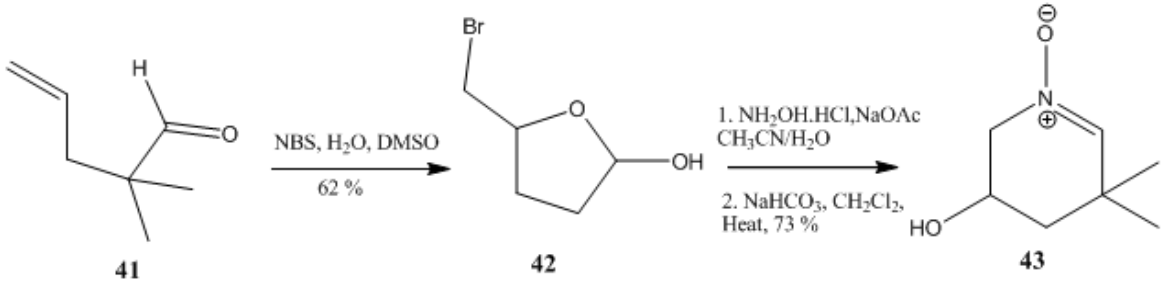
Scheme 14.

Bromocyclization of γ,δ-unsaturated oximes (**39**) affords the corresponding bromomethylpyrroline-N-oxides (**40**) (Scheme 15). Reversal of steps, that is addition of Br/OH to the C=C bond of the unsaturated aldehyde (**41**) first, followed by oximation, opens access to six-membered nitrones (**43**) (Scheme 16) [48].



39 **40**

Scheme 15.



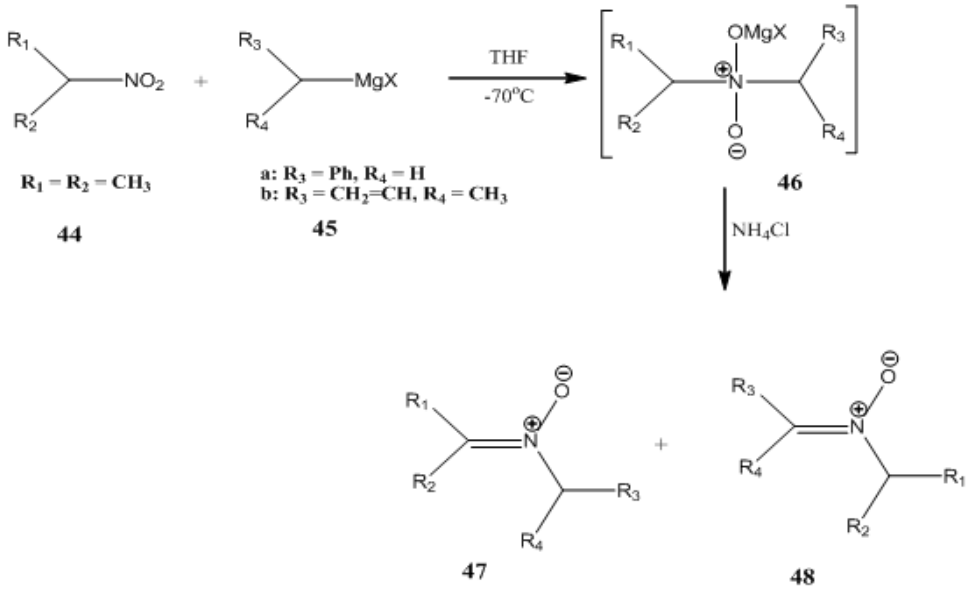
41 **42** **43**

Scheme 16.

1.3.2.3 Synthesis from nitro compounds

Nitrones can be obtained in good yields from the addition of benzyl and allyl Grignard reagents to aryl- and alkylnitro compounds. This reaction proceeds chemoselectively; carbonyl groups and other reactive electrophilic groups are not affected by the reaction conditions. Double bond stereochemistry is determined by the nature of the

employed Grignard reagent. Benzylmagnesium halides give exclusively Z -isomers of nitrones (**47**) and (**48**), whereas 2-butenylmagnesium chloride gives nonconjugated Z-nitrones with the predominance of E-isomers in the conjugated nitrone (**174**) **(Scheme17)** [49-51].



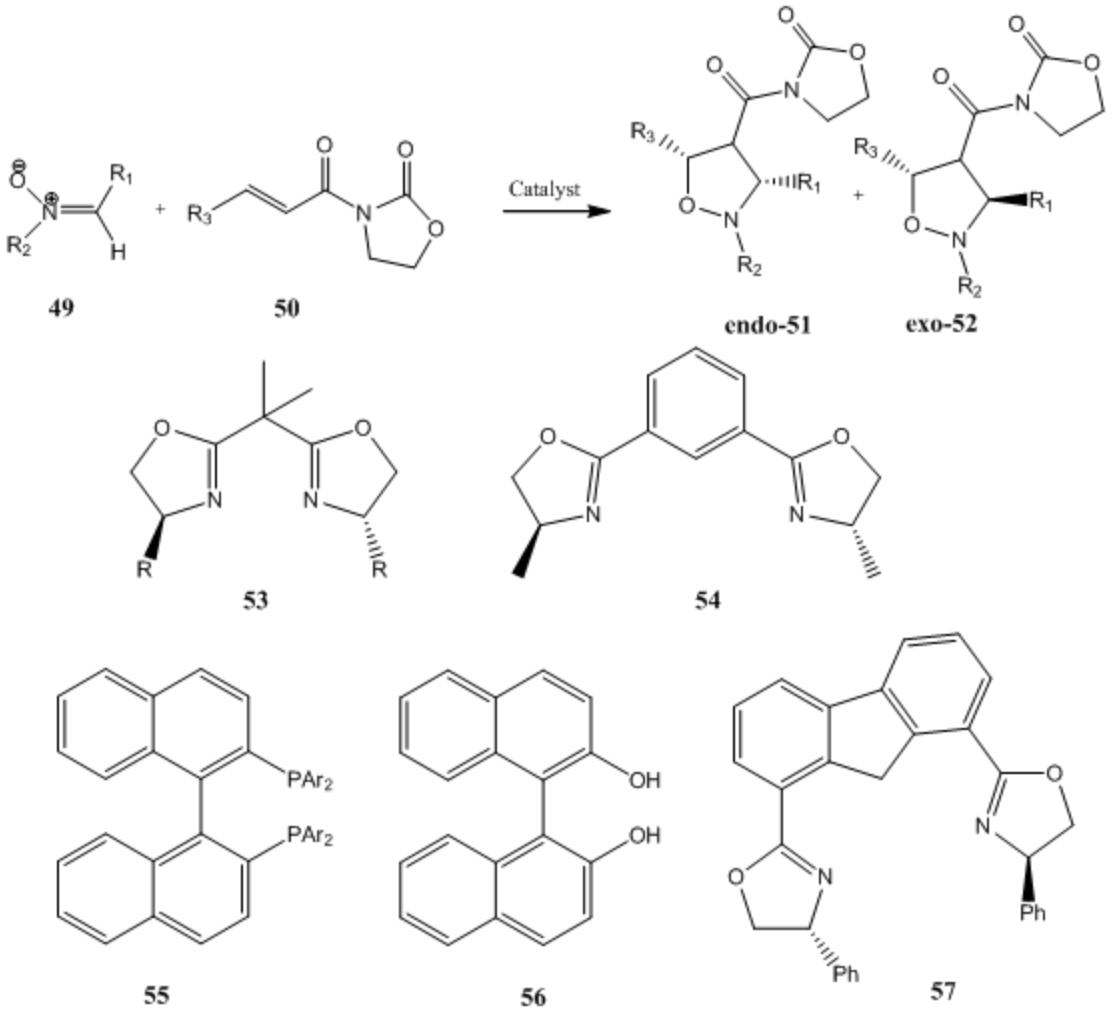
Scheme 17.

1.4 Asymmetric induction in nitrone cycloaddition

Asymmetric Induction describes the preferential formation in a chemical reaction of one enantiomer or diastereomer over the other as a result of the influence of a chiral feature present in the substrate, reagent, and catalyst. The addition of a nitrone to an alkene or alkyne is a prominent transformation in organic synthesis. Over the past two decades the intense study of enantioselective 1,3-dipolar cycloaddition methodologies has provided organic chemists with the tools necessary to synthesize a variety of chiral heterocycles in highly enantio-enriched forms. Over the years a variety of chiral Lewis acids have been

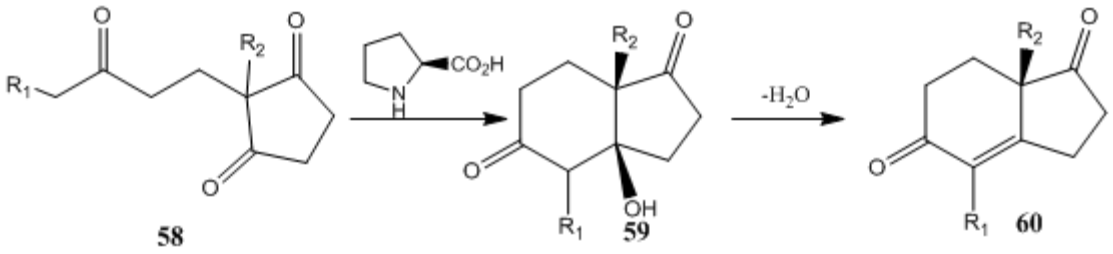
evaluated for dipolar cycloadditions. The most successful of these have employed copper, silver, nickel, aluminum, zinc, and lanthanide Lewis acids, generally in combination with one of the privileged classes of chiral ligands such as the bisoxazolines, BINAPs, and Pyboxs. Chiral copper(I) and (II) salts figure prominently in the development of enantioselective 1,3-dipolar cycloaddition reactions (Scheme 18) [52-54].

All of the enantioselective reactions described so far have involved catalysts composed of enantiomerically pure ligands coordinated to various metal-salts. Those catalysts often have to be used under dry conditions under an inert atmosphere. A more easily managed, metal-free catalyst gives operational and economical advantages over the ones containing metals. Therefore, organocatalysis has become a very active research field at present. Organocatalysts are often low molecular weight compounds readily available from inexpensive starting materials. They can in general be reused in a convenient manner. Because organocatalysts do not contain any heavy metals, they are, in general, more environmentally friendly than most chiral Lewis acid catalysts. Moreover, organocatalysed reactions can often be conducted under air and even in wet solvents [55,56].



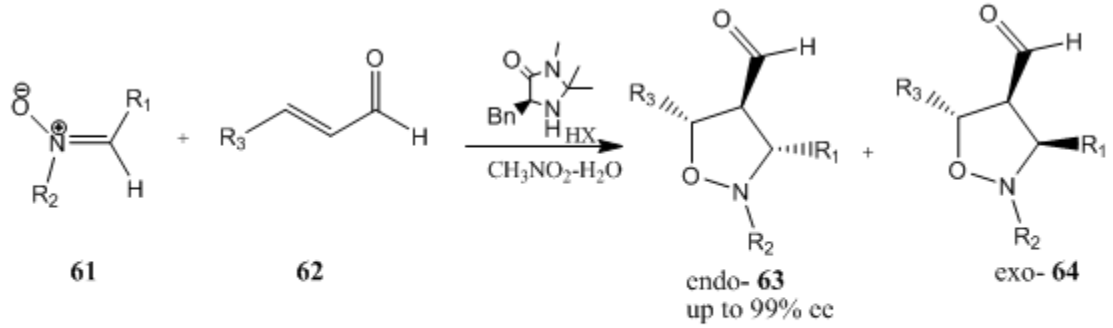
Scheme 18.

A milestone in the field of organocatalysis is the development of the enantioselective Robinson annulation of triketones of type **58** catalysed by proline (Scheme 19). Thus, in the presence of this naturally occurring amino acid (i.e. proline), such triketones undergo Robinson annulation to give chiral nonracemic bicycles **59**, which, after dehydration, furnish compounds of type **60**. This approach has opened a new route for enantioselective syntheses of steroids and other natural products such as taxol [57,58].



Scheme 19.

Since the discovery of the proline catalyzed Robinson annulation reaction discussed above, organocatalysis has become a rapidly growing research area in organic chemistry. In the field of 1,3-dipolar cycloaddition reactions, MacMillan *et al.* have been the first to explore organocatalysis. They have developed a general protocol for the enantioselective syntheses of isoxazolidines from nitrones of type **61** and α,β-unsaturated aldehydes **62** catalysed by the phenylalanine derived organocatalyst (Scheme 20) [59,60].



Scheme 20.

1.5 Application of nitrone cycloaddition reaction

The impact of dipolar cycloaddition reactions in the area of heterocyclic synthesis is in many ways comparable to that of Diels–Alder reactions on carbocyclic synthesis. In fact, the availability of various classes of dipoles and dipolarophiles has allowed a greater

degree of versatility. The discovery of new dipolar species was followed by applications of their reactions in targeted syntheses. Even though all dipolar cycloaddition reactions are, in principle, closely related processes, their applications are seldom discussed together in the chemical literature. The main reason for this anomaly is the vast variety of heterocyclic systems produced in such reactions. Discussions on heterocyclic synthesis generally follow a product-class-based approach. Although convenient, such an approach fails to address the underlying similarities of the various processes involved. There has been no concerted attempt to categorize various dipolar cycloadditions used in the synthesis of natural products, apart from an excellent book edited by Padwa. Because the total syntheses of various natural products and other bioactive substances via asymmetric 1,3-dipolar cycloaddition reactions of nitrones are numerous, only a few examples will be presented here [61-63].

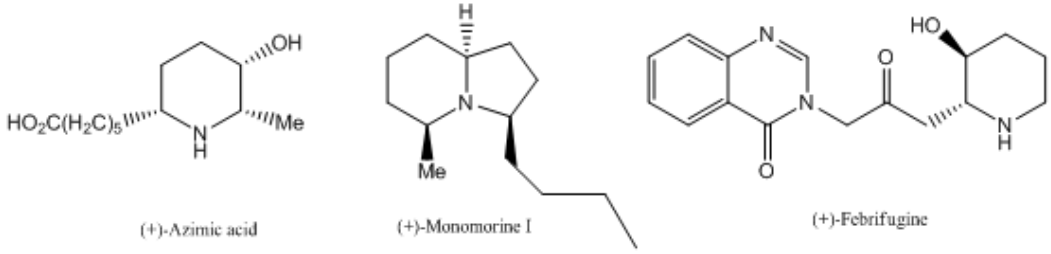
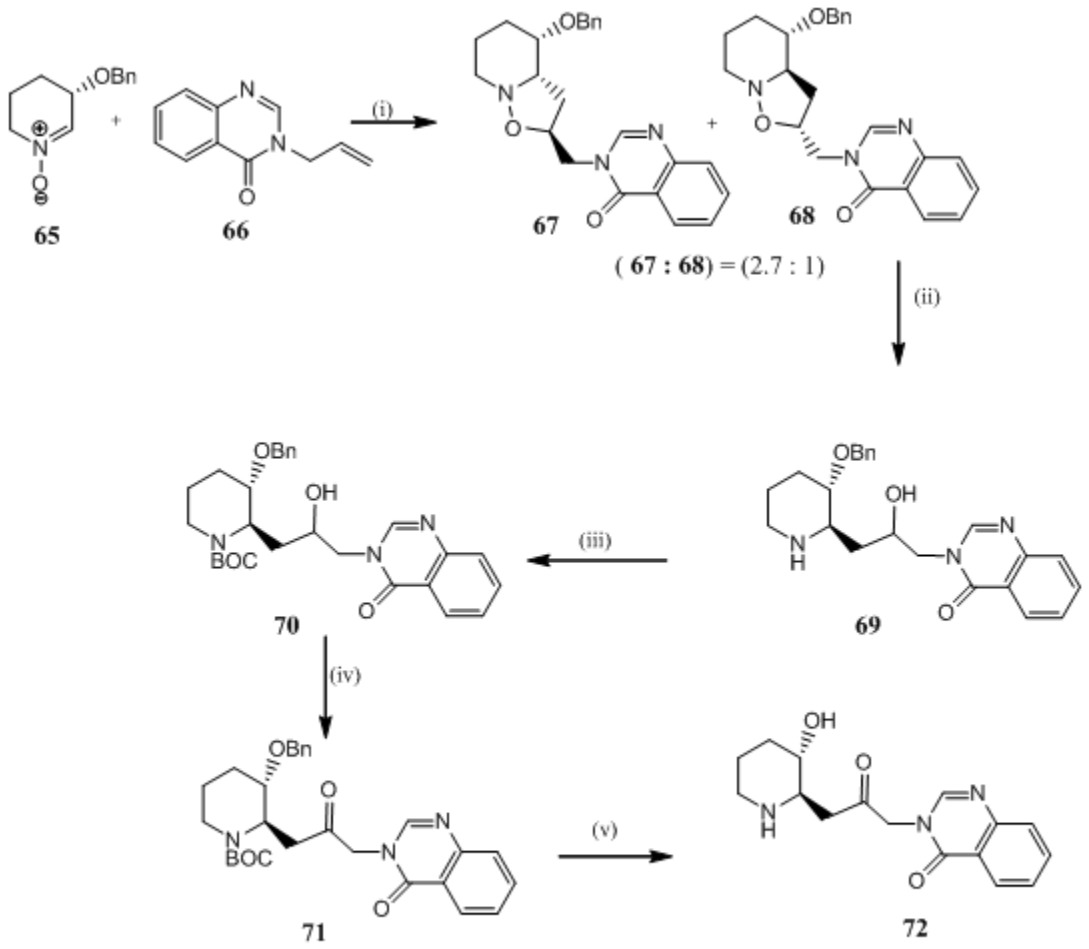


Figure 1.

Caprio *et. al*. synthesized trans-2-Substituted-3-hydroxypiperidines to form the core structure of a diverse range of alkaloids of biological interest, such as the anti-malarial alkaloid (+)-febrifugine *via* nitrone cycloaddition of (S)-3-benzyloxy-3,4,5,6-tetrahydropyridine N-oxide from L-glutamic acid (Scheme 21) [64].

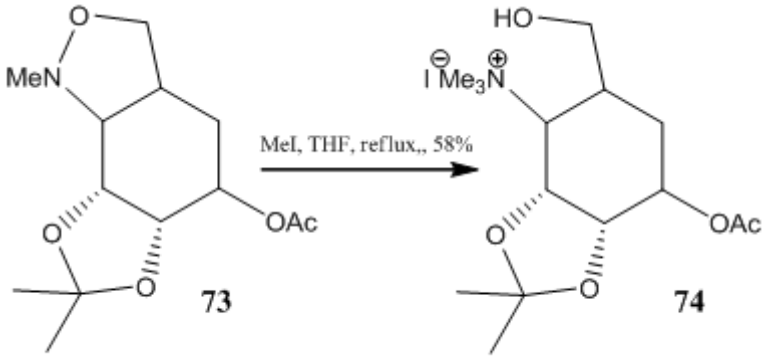


Scheme 21. Reagent and condition: (i) PhMe, reflux, 24 h, **67** 48%, **68** 18%; (ii) Zn, HOAc,reflux, 5h, 53%; (iii) BOC_2O, Et_3N, CH_2Cl_2, 20h, 80%; (iv)Dess-Martin periodinane, pyridine, CH_2Cl_2, 2h, quant.; (v)$_6$ M HCl(aq), reflux, 40 min, 67%.

Isoxazolidines are structural key moieties in many bioactive substances and herbicides. Because they are also easily ring opened to the corresponding aminoalcohols, they can serve as attractive building blocks for the construction of other natural products and bioactive substances. Isoxazolidines are also building blocks for the preparation of chiral ligands which are used in enantioselective transformations [60-63].

N-O bond cleavage in isoxazolidines is a very important reaction as it can be transformed to many intermediates which are useful in several total syntheses. Three

different reactions for N-O bond cleavage are mentioned in the literature. The first reaction is the normal reduction using any reducing agent such as Zn/HOAc, $LiAlH_4$ (Scheme 21) [64]. The second reaction is MCBPA ring opening to produce the second generation of nitrones (Scheme 11) [35, 36]. The last reaction is a quaternrization of the isoxazolidines by means of any alkyl halides (Scheme 22). The importance of these three reactions is its application in synthesis by the liberation of the masked functionality in the resulting isoxazolidines [65].



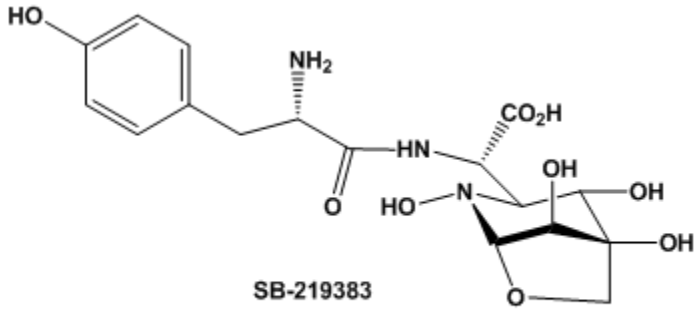
Scheme 22

CHAPTER 2

2.1 Literature Review

Nitrones are very useful tools in the construction of structurally complex molecules and particularly biologically active nitrogen-containing compounds. The cyclic nitrones, in the absence of E ⇄ Z isomerization enjoy a higher degree of stereoselectivity in compare to its acyclic counterpart. Various types of methods in the literature described the preparation of cyclic nitrones, including the oxidation of cyclic amines, hydroxylamines, imines, intramolecular condensation of ω-hydroxylaminocarbonyl derivatives, and cyclization of ω-unsaturated oximes.[2f]

Six-membered cyclic nitrones are considered as an attractive building block for a natural product synthesis. The natural product **SB-219383**, isolated from a *Micromonospora* sp. NCIMB 40684, is a potent and selective inhibitor of bacterial tyrosyl tRNA synthetase (YRS) and as such is a potential lead for new antibacterial agents. **SB-219383** contains a unique bicyclic hydroxyamino sugar moiety (Figure 2).



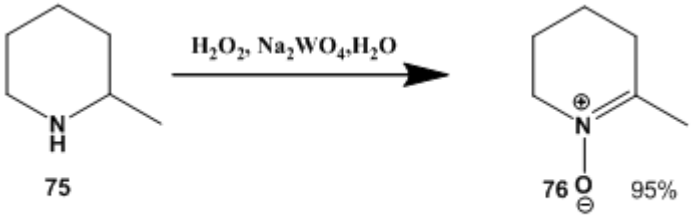
SB-219383

Figure 2.

Both indolizidine and quinolizidine alkaloids [66] contain the piperidine ring, this is why it's very useful to start with this type of ring as a starting material. Many studies have been done on a substituted 3,4,5,6-tetrahydropyridine 1-oxide. So, it's worth to mention some of these studies according to the pattern of substitution on the ring.

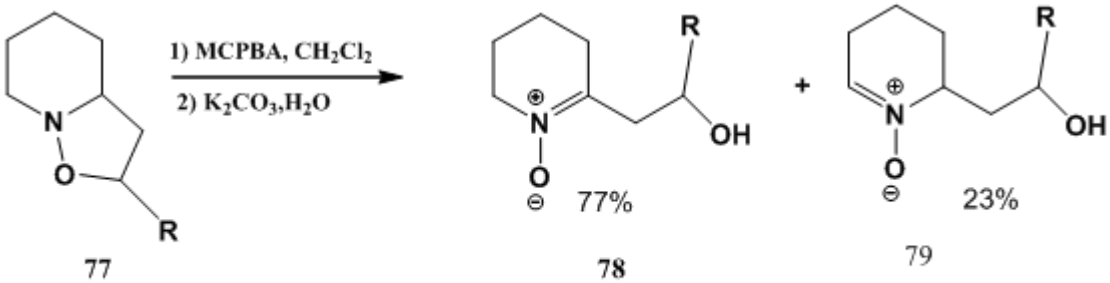
2.1.1 2-Substituted tetrahydropyridine N-oxide

Extensive works on this class of nitrone were mentioned in the literature. Nitrone **76** is prepared by an oxidation of the corresponding amine **(75)** in presence of a tungsten catalyst (Scheme 23) [67-69].



Scheme 23.

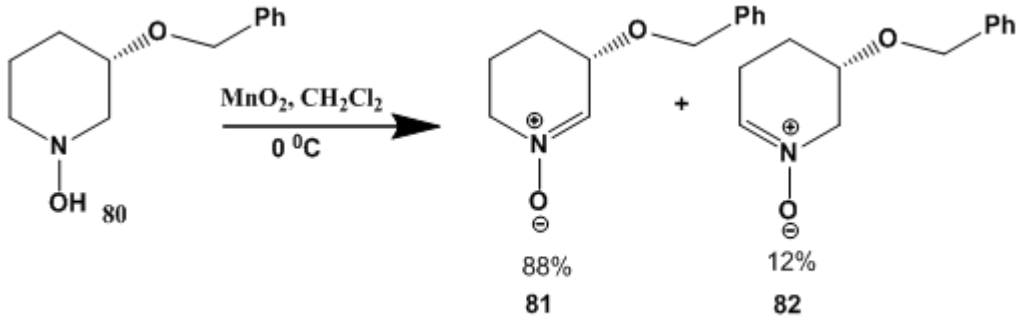
Some of these nitrones **(78, 79)** are generated by peracid induced ring opening of the cycloaddition products **(77)** (Scheme 24) [17].



Scheme 24.

2.1.2 3-Substituted tetrahydropyridine N-oxide

Substitution at C-3 of the tetrahydropyridine N-oxide has been mentioned in the literature [25]. Nitrone **(81)** is prepared by an oxidation of corresponding hydroxylamine (Scheme 25). Different types of substitution products on the ring have been synthesized and a cycloaddition reaction was done to examine the regio- and stereoselectivity of the adducts **(83-85)** [70-72].

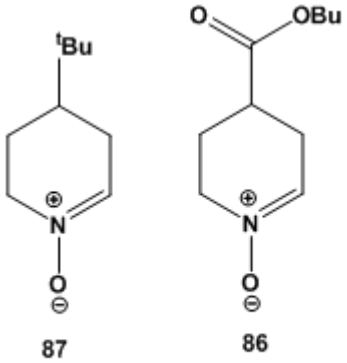


Scheme 25.

c

2.1.3 4-Substituted tetrahydropyridine N-oxide

Only two studies on six-membered nitrone containing a substituent farthest from the nitrone moiety, i.e., at the C(4) position have been reported [73,74]. The recent study reports the kinetic and stereoselectivity of the addition reaction of a C(4)-substituted cyclic nitrone **(86)** with various alkenes .

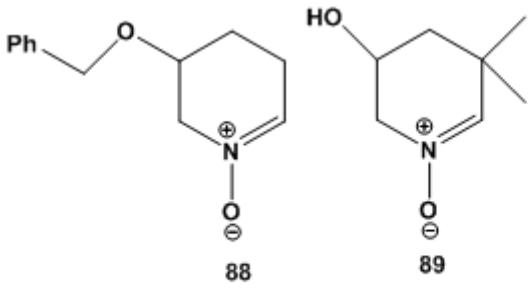


87 86

Figure 4.

2.1.4 5-Substituted tetrahydropyridine N-oxide

Also, few studies on six-membered nitrones **(88**, **89)** containing a substituent at the C(5) position have been reported [75].



88 89

Figure 5.

2.1.5 6-Substituted tetrahydropyridine N-oxide

Cycloaddition reactions involving 6-substituted 3,4,5,6-tetrahydropyridine 1-oxides **(90-92)** and alkenes are reported to give single cycloadducts in a regio-, face-, and stereo-selective manner [76,77].

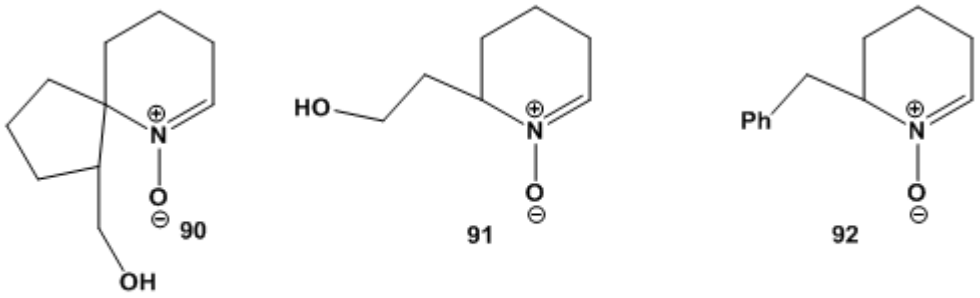


Figure 6.

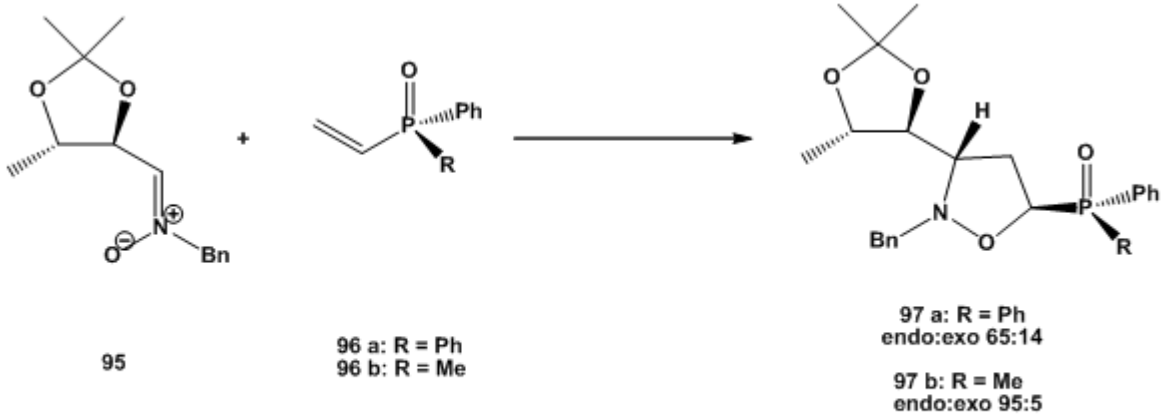
There have been much interest in the asymmetric synthesis of isoxazolidines using 1,3-dipolar cycloaddition reaction. Intermolecular nitrone olefin cycloaddition reactions leading to optically active isoxazolidines have been carried out by several workers using chiral starting material (nitrone or alkene or both) and by metal-catalyzed reactions. Several groups have also reported a reaction of alkenyl nitrone leading to optically active products (Schemes 8-11).

Nitrones **(93)**, bearing 1-phenylethyl substituent at the nitrogen atom and with different substituents at the carbon atom, have been subjected to 1,3-DC reactions with styrene **(94)** [33b,c]. The reactions proceed to give a mixture of the exo and endo isomers in ratios between 68:32 to 87:13 Scheme 26.

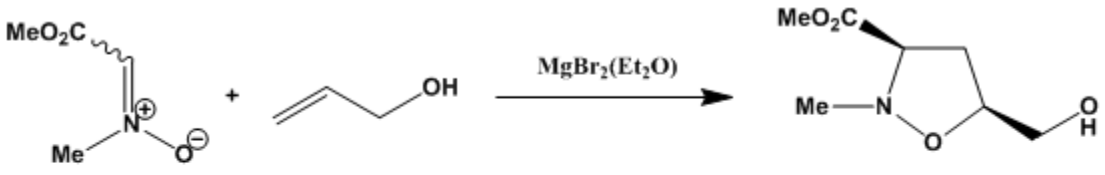
The chiral group can be located at the carbon atom. Brandi *et al*, have studied the nitrone cycloaddition of chiral α,β-dialkoxynitrones **(95)** with vinylphosphine oxide **(96a,b)**. The reaction of **(96a)** gave a 65:14 mixture of the endo: exo isomers. The endo isomer was formed with a high diastereofacial selectivity of 94% de. However, the reaction with **(96b)** proceeded to form **(97b)** with a high degree of endo selectivity with diastereofacial selectivity of 96% de (Scheme 27) [78].

Kanemasa *et al.* [79] studied the reaction of allylic alcohols with nitrones in the presence of Mg(II) salts, $ZnBr_2$, $TiCl_2(O^iPr)_2$, or $BF_3.Et_2O$. The reaction of the following nitrone **(97)** with allyl alcohol afforded the *cis* and *trans* isomers in a ratio of 44:56. In the presence of 1 equiv $MgBr_2.Et_2O$ the *cis* isomer **(98)** is obtained as the sole product (Scheme 28). In recent years, the asymmetric nitrone cycloaddition reactions involving the intramolecularly H-bonded nitrone (Scheme 29) is receiving increasing attention owing to its efficacy in transferring chirality to the newly created stereocenter at C(4) and C(5) of the cycloadducts isoxazolidines [79].

ccc

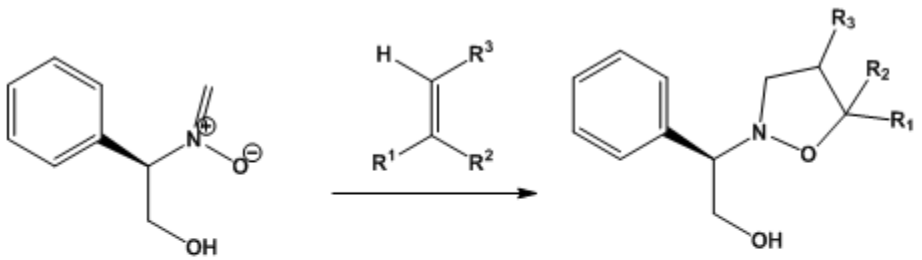


Scheme 27.



98 99

Scheme 28.



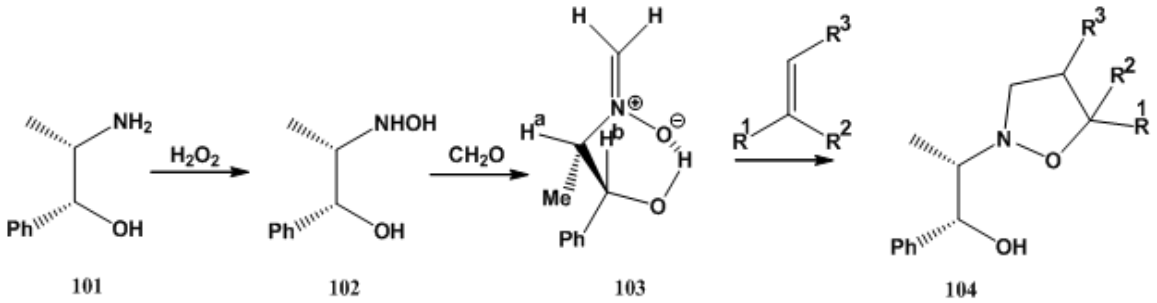
99 100

Scheme 29.

2.2. Objectives

After examining the precedent literature on DC, the objectives of the proposed study were outlined under (i)-(ix).

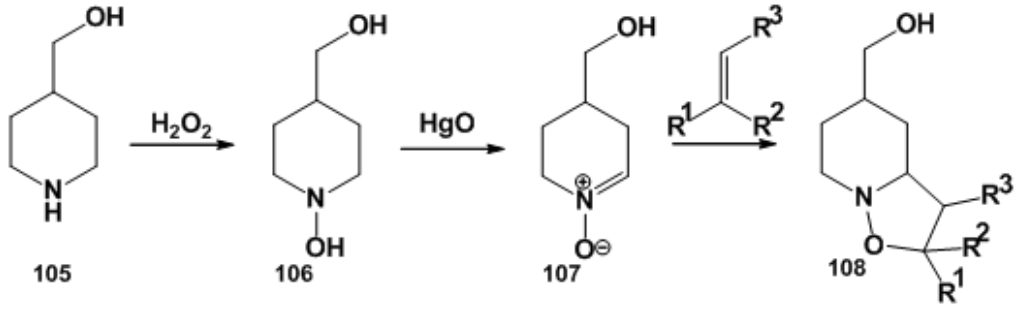
i) Synthesis and stereochemical analysis of some norephedrine-derived isoxazolidines (Scheme 30).



101 102 103 104

Scheme 30.

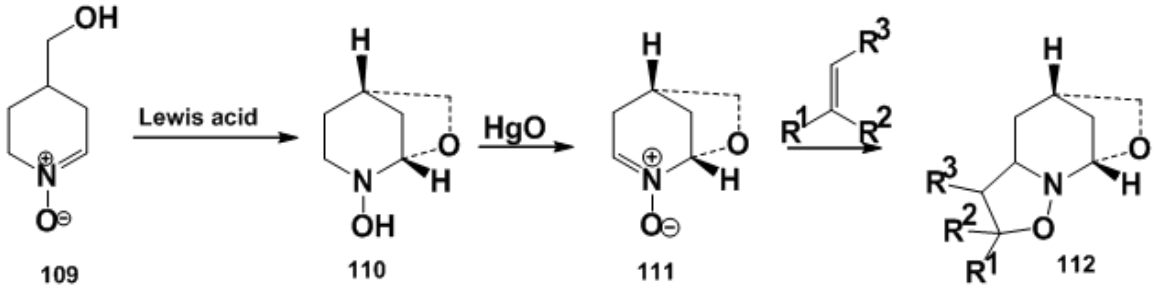
ii) Synthesis of 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide (**107)** and its stereochemistry of cycloaddition to various alkenes (Scheme 31).



105 106 107 108

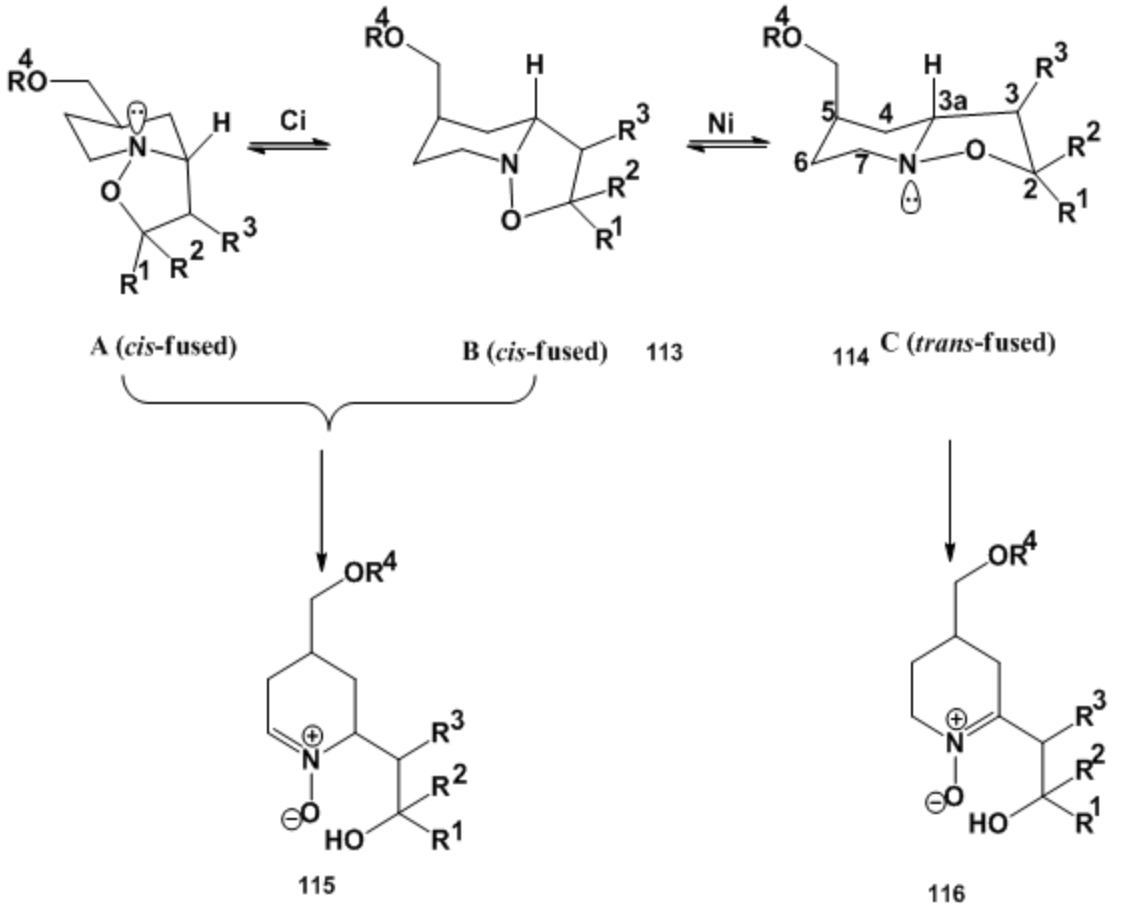
Scheme 31.

iii) Synthesis of novel bicyclic nitrone **(111)** and its stereochemistry of cycloaddition to various alkenes (Scheme 32).



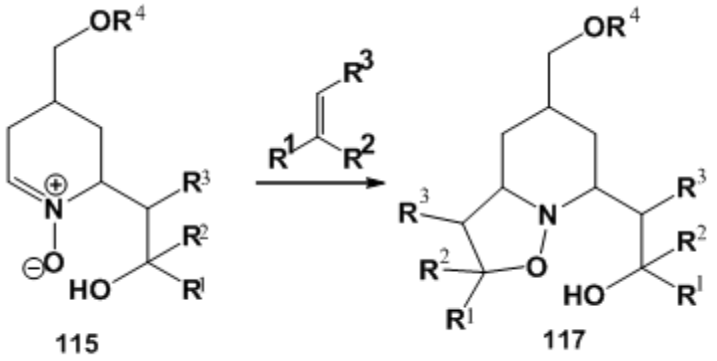
Scheme 32.

iv) Study of conformational equilibria in cycloaddition product isoxazolidines **(113)** to shed light on the composition of peracid induced ring opening to obtain second generation aldo-**(115)** and keto-nitrones **(116)** (Scheme 33).



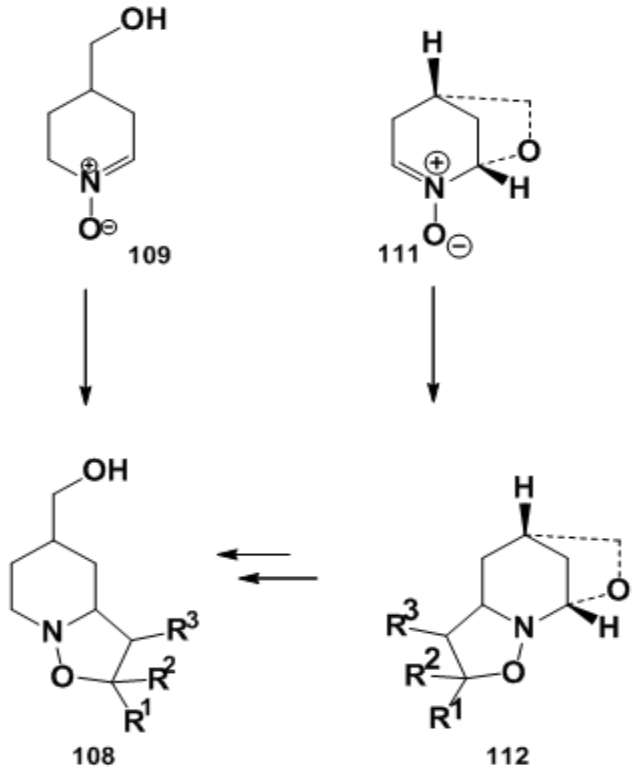
Scheme 33.

v) Stereochemistry of cycloaddition of second generation aldonitrones **(115)** to various alkenes (Scheme 34).



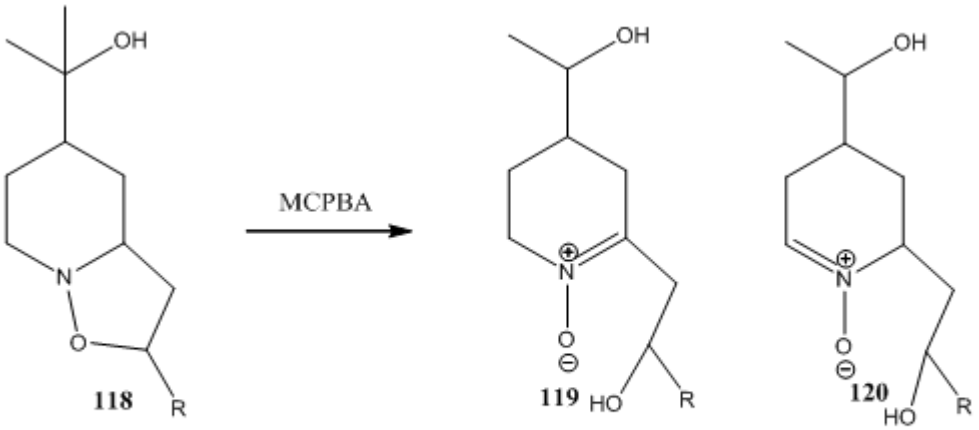
Scheme 34.

vi) Conversion of tricyclic adducts **(112)** to bicyclic adduct (**108)** to investigate the possible reversal of stereochemistry in the addition of the mono-**(109)** and bicyclic nitrone (**111)** (Scheme 35).



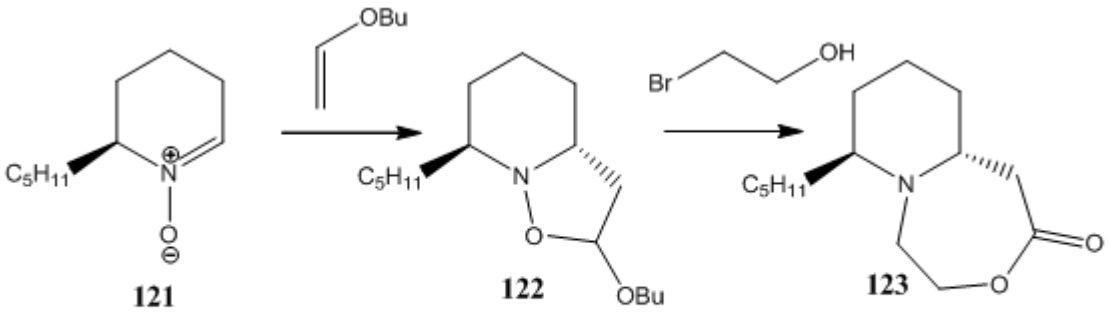
Scheme 35.

vii) Study the effect of the bulkier tertiary substituent at C(4) on the *cis-trans* ratio of the cycloadducts and second-generation aldonitrones *via* peracid induced ring opening of the cycloadducts (Scheme 36).



Scheme 36.

viii) Due to the high stereoselectivity of the cycloaddition reaction, and as an application in the synthesis of natural product, the total synthesis of epi-calvine **(123)** will be attempted using the reaction scheme as outlined (Scheme 37).



Scheme 37.

ix) Use of ^{1}H, ^{13}C NMR spectroscopy, elemental analyses, mass spectrometry, and X-ray crystallography to characterize the synthetic products.

CHAPTER 3

Synthesis and stereochemical analysis of some norephedrine-derived isoxazolidines

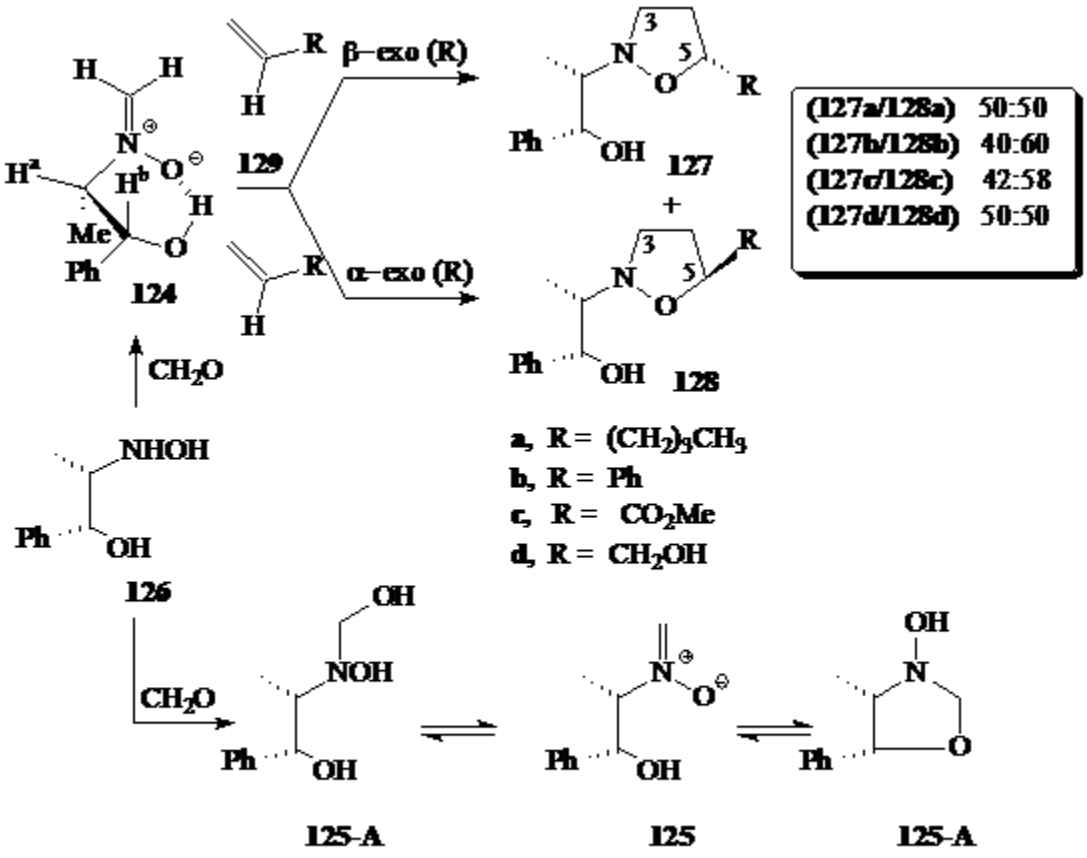
Summary:

The diastereoselectivity in the cycloaddition reactions of several mono- and disubstituted alkenes with a (-)norephedrine-derived methylenenitrone has been investigated. The stereochemical analysis of the addition products (i.e. isoxazolidines) has been carried out by X-ray, NMR and chemical conversions. The NMR spectra of the isoxazolidines at low temperatures indicated the presence of either a single or a predominant invertomer. The stereochemistry of the invertomers and nitrogen inversion barriers are determined using complete line-shape analysis and their dependence on solvent is discussed.

3.1 Introduction

1,3-Dipolar cycloaddition reaction of nitrones is the best chemical template for the construction of isoxazolidine ring; efficient incorporation of multiple stereocentres makes it an efficient key step in the synthesis of a great many natural products of biological interest [2]. In recent years, focus has been shifted towards asymmetric nitrone cycloaddition reactions, the efficiency of which very much depends on the ability of the chiral auxiliary to effectively transfer chirality to the newly created stereocenters [2]. Even though the nitrone cycloaddition reactions of C,N-disubstituted nitrones have been studied in great detail [2] , the chemistry of chiral (or even achiral) N-substituted nitrones (i.e. methylenenitrones) has only been investigated to a limited extent [80]. Here we report, for

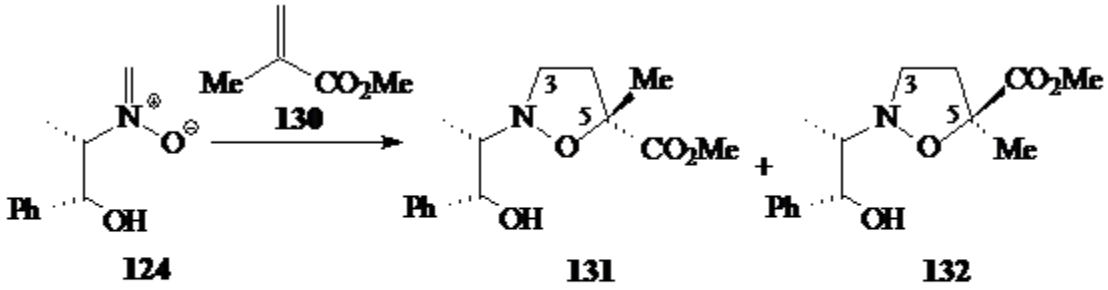
the first time, the stereochemical features associated with the cycloaddition of a norephedrine-derived chiral methylenenitrone **124** (Scheme 38) with several mono- and 1,1-disubstituited alkenes. The study would reflect the scope and limitations associated with the addition reactions of this important and readily accessible optically pure methylenenitrone. The NMR spectroscopy is utilized to examine the nitrogen inversion process and determine the configuration of the cycloadducts (isoxazolidines).



Scheme 38.

3.2 Results and Discussion

Each nitrone (**124**)-alkene cycloaddition with **129** (or **130**) proceeded regiospecifically to afford a separable mixture of diastereomeric isoxazolidines **127** and **128** (or **131** and **132**), the compositions of which are given in (Schemes 38 and 39).



Scheme 39.

Since the nitrone is optically pure, the isoxazolidines differ only in the configuration of the C(5) substituents. The nitrone **124** is expected to assume the conformation as depicted in Scheme 38. The planar nitrone functionality is in Ha-eclipsed conformation **127** having Me and PhCHOH on the α- and β-faces, respectively. The J_{ab} value of 5.5 Hz, corresponding to a torsional angle of 40.5° as determined by Karplus rule, supports the gauche orientation between Ha and Hb. Since both the faces of the dipole, in the vicinity of N, have substituents, addition reaction does not offer any clear cut face selectivity. Sterically favored α-exo (R) or β-exo (R) mode of attack may happen with equal ease thereby giving the isoxaolidines **127** and **128** in almost equal yields (Scheme 38).

Since the addition reaction of methyl acrylate (**129c**) was found to have a preference to give the isoxazolidine **128c** by an α-*exo* (CO2Me) mode of approach

Table 2
^{13}C NMR Chemical Shifts of compounds Studied in $CDCl_3$ at -40°C

(Scheme 38), the major adduct in the addition reaction of methyl methacrylate (**130**) was similarly assigned the configuration of **132** obtained by a similar α-exo (CO_2Me) mode of attack (Scheme 39). However, in the absence of X-ray analysis (owing to difficulty in

Compound	Invertomer[a]	C-3	C-4	C-5	C-OH	N-C	Me
127a	Major (*RSR*)	52.32	33.90	76.75	72.59	65.68	10.88
	Minor (*RSS*)	52.06	33.81	77.50	74.81	67.26	7.12
128a	Major (*RSR*)	53.13	33.61	77.48	72.31	68.02	10.75
	Minor (*RSS*)	51.87	34.24	74.38	73.96	65.93	7.42
127b	Major (*RSR*)	53.02	37.48	77.57	72.44	66.31	10.73
	Minor (*RSS*)	52.38	36.97	78.95	75.68	66.71	6.44
128b	Major (*RSR*)	53.90	36.93	78.77	71.98	68.15	10.65
	Minor (*RSS*)	52.54	37.51	78.85	74.70	65.99	7.45
127c	(*RSR*)	51.63	32.90	73.38	72.03	65.79	11.07
128c	Major (*RSR*)	51.78	32.98	75.09	71.68	66.92	10.48
	Minor (*RSS*)	50.59	32.18	76.20	74.05	64.46	5.14
127d	(*RSR*)	53.03	29.44	77.47	71.71	67.30	10.36
128d	Major (*RSR*)	53.64	30.03	77.67	71.61	67.98	10.62
	Minor (*RSS*)	52.26	29.26	78.07	74.72	66.09	7.37
131	(*RSR*)	52.50	39.13	81.11	71.90	65.81	10.80[b]
132	Major (*RSR*)	52.08	39.02	82.17	72.06	66.31	10.55[c]
	Minor (*RSS*)	51.06	38.10	81.63	76.91	64.06	4.00[d]

[a]Absolute configuration of the chiral centers as defined in Schemes 38 and 39.
C(5) Me at [b]22.82, [c]24.29, [d]22.95 ppm

getting crystalline material), the configuration of the adduct could not be confirmed.

During the course of the structural investigation of the isomeric isoxazolidines, it was observed that the isoxazolidines were present either as a single invertomer or an equilibrating mixture of two invertomers in a ~80:20 ratio at lower temperatures in $CDCl_3$. Slow nitrogen inversion in most of the isoxazolidines has been observed to give broadened peaks in ^1H and ^{13}C spectra recorded at ambient temperature. On lowering the temperature, the spectral lines became sharper and showed two distinct forms of the compound. Around -10°C, the ^1H NMR spectra of these compounds showed well separated signals for the two invertomers. Integration of the relevant peaks gives the population trends in these systems. The ^{13}C chemical shifts were assigned on the basis of DEPT experiment results, general chemical shifts arguments and consideration of substituent effects, and are given in (Table 2).

The nitrogen inversions barriers were determined using NMR band shape analysis. The proton spectra were used in the calculation of barriers in all compounds. The complete band shape analysis yielded the rate constants and the free energy of activation using Eyring equation. The activation parameters $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated from plots of ln(k/T) vs. 1/T. It is well known [5] that NMR band shape fitting frequently gives rather large but mutually compensating errors in $\Delta H^{\neq}$ and $\Delta S^{\neq}$ and as such their values are not reported here. However, band shape fitting is viewed as a method of getting rather accurate values of $\Delta G^{\neq}$ (probably within ± 0.3 kJ/mol) in the vicinity of the coalescence temperature. The $\Delta G^{\neq}$ values calculated at 0^oC are reported in Table 3, along with the invertomer ratios and ΔG^o values.

Table 3.

Free Energy of Activation ($\Delta G^{\neq}$) for nitrogen inversion, Ratio of the Invertomers, and standard Free Energy Change (ΔG^{o}) for major ↔ minor isomerization in $CDCl_3$

Compound	$CDCl_3$		
	$\Delta G^{\neq}$ (kJ/mol)[a]	Invertomer Ratio	ΔG^{o} (kJ/mol)[b]
127a	59.5	83:17	+3.1
128a	59.4	89:11	+4.1
127b	59.4	88:12	+3.9
128b	59.8	90:10	+4.2
127c	–	100:0	–
128c[c]	56.9	83:17	+3.1
128c	58.5	79:21	+2.6
128c[c]	58.5	87:13	+3.7
127d	–	100:0	–
128d	60.3	84:16	+3.2
131	–	100:0	–
132	56.5	63:37	+1.0

[a]At 0°C. [b]At -40°C. [c]in CD_3OD

Both the *cis*-1,3-dimethylcyclopentane and *cis*-1,3-dimethylcyclohexane are known [81] to be more stable than their trans counterparts by an enthalpy difference of 2.3 kJ/mol and 7.1 kJ/mol, respectively. The slight preference for the *cis* isomer in cyclopentane may be attributed to the disposition of the substituents in the pseudoequatorial orientations. The 2,5-disubstituted isoxaozolidines, however, have been found to have a slight preference

for the trans-invertomers [82]; shortened bond lengths due to the presence of two heteroatoms are expected to augment the steric congestion between the cis substituents. The conformation of 5-membered ring system is indeed very complex to elucidate with some certainty. The complexity arises from the fact that changing the size of the substituent may lead to change in conformation (half chair/envelope/near planar) and the flap of the envelope. Earlier works [82] on 2,5-disubstituted isoxazolidines revealed the trans-invertomer as the major isomer. The 2-methyl-, 2-isopropyl-, and 2-^{t}butyl-5-^{t}butyldimethylsiloxymethylisoxazolidines were found to have the trans- and cis-invertomers in a ratio of 53:47, 55:45 and 63:37, respectively. The compounds studied in this work are sterically similar to the 2-isopropylisoxazolidines since they also contain a secondary alkyl substituent at the 2-position (Scheme 38).

To confirm the stereochemistry, adducts **128b** and **128c** were subjected to X-ray crystallographic analysis; the ORTEP representations are shown in (Figures 7 and 8). The stereochemistry of the methyl acrylate adducts **127c** and **128c** were then correlated to allyl alcohol adducts **127d** and **128d** by conversions of the former isomers to the later by reduction with lithium aluminum hydride. It has been observed that the minor isomers (**127b**, **128c**) in the addition reactions of styrene or methyl acrylate always eluted first during the silica gel chromatography. As a result, in the addition reaction of 1-hexene, adduct eluted first was given the configuration of **127a**. The X-ray analyses revealed the existence of both the adduts **128b** and **128c** in the cis invertomeric form. The chemical shift difference between the isomers for a particular ring carbon is generally less than 1 ppm for most carbons and as such the C-13 shifts are not very sensitive to the difference

Table 4. ^{1}H NMR Chemical Shifts of C**H**$_3$C–N and PhC**H**O signals of the compounds Studied in $CDCl_3$ at -40°C

Isoxazolidine	C**H**$_3$C–N		PhC**H**O	
	Major[b] δ (ppm)	Minor[c] δ (ppm)	Major[b] δ (ppm)	Minor[c] δ (ppm)
127a	0.81	1.00	5.26	5.14
128a	0.81	Overlapped	5.35	5.00
127b	0.85	1.09	5.43	5.22
128b	0.94	1.02	5.43	–[a]
127c	0.78	–[b]	5.38	–[b]
127c[c]	0.77	1.02	5.37	5.17
128c	0.84	0.95	5.45	5.18
128c[c]	0.80	1.01	5.47	5.17
127d	0.85	–[b]	5.43	–[b]
128d	0.88	1.00	5.42	5.02
131	0.73	–[b]	5.39	–[b]
132	0.80	0.94	5.39	5.21

[a]overlapped. [b]No minor invertomer. [c]in CD_3OD

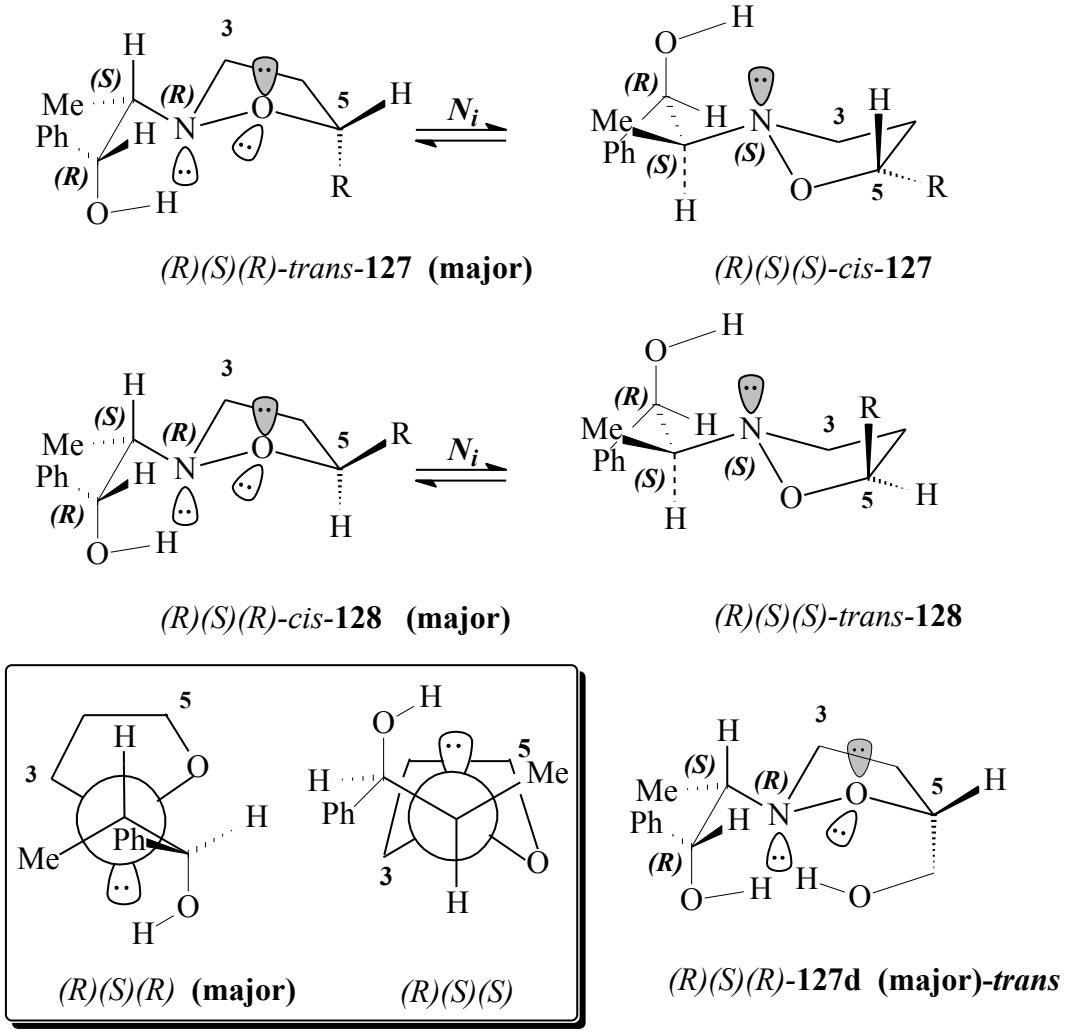
in the isomeric configurations (Table 2). This is not surprising in view of the fact that the five-membered ring does not have the well-defined conformation of six-membered systems. However, one striking difference in the ^{13}C chemical shift values of CH_3C–N was observed; the signals for the major invertomers appeared at δ 10.7 ± 0.2 ppm, while the minor signal appeared at δ 6.8 ± 0.9. The C-3 and C-OH of the major invertomers invariably appeared downfield and upfield, respectively, in compare to the minor

invertomers (Table 2). The benzylic proton NMR signals for all the major invertomers appeared downfield than the PhCHO of the minor invertomers (Table 4). The methyl protons in $CH_3C–N$ of the major and minor invertomers appeared upfield and downfield, respectively, in all the compounds studied. Similar trend in the chemical shift values of PhCHO and $CH_3C–N$ protons (Table 3) and the $CH_3C–N$, C-3 and C-OH carbons (Table 1) between the major and minor invertomers strongly suggest the similarity in the configuration among all the major invertomers (or among all the minor invertomers). As supported by X-ray analyses, all the dominant or sole nitrogen invertomers are believed to have the identical configuration of (R), (S), and (R) at the three chiral centers at benzylic C, exocyclic C attached to nitrogen, and N, respectively.

X-ray analyses revealed that the proton in exocyclic CH-N is anti to the nitrogen lone pair as depicted in (Scheme 40); the arrangement will have the lower number of gauche interactions (two in these cases) around the C-N bond. The protons in the exocyclic CH-N and PhCHO are not in expected anti dispositions; the torsional angle between them is found to be 63.3° in **128c** as a result of their gauche orientations (Scheme 40 and Figure 8). Similar orientation is observed in the ORTEP diagram of **128b** (Figure 7).

Such an orientation will lead to a very low coupling constant ($J \approx 1.5$ Hz) between these protons as calculated using Karplus equation. The appearance of PhCHO proton of both the invertomers as a singlet (i.e. $J \approx 0$ Hz) in the ^1H NMR spectrum in $CDCl_3$ or CD_3OD confirmed the gauche orientation between these protons in solution as well as solid state. Such an orientation may be helpful in establishing intramolecular H-bond between the OH and nitrogen lone pair as depicted in (Scheme 40). The sum of Van der

Waal radii of H,N is known to be 2.75 Å, while the observed distance of 2.44 Å in **128c** (Figure 8) suggest the presence of intramolecular H-bond.



Scheme 40.

A look at the Newman projections (Scheme 40) revealed that the Me and C-3 are in the gauche conformations in the major invertomers, while they remain anti in the minor invertomers. We cannot offer a rationale, at this stage, for the considerable upfield shift by ~4 ppm for the methyl carbons in the methyl/C-3 anti-oriented minor invertomers.

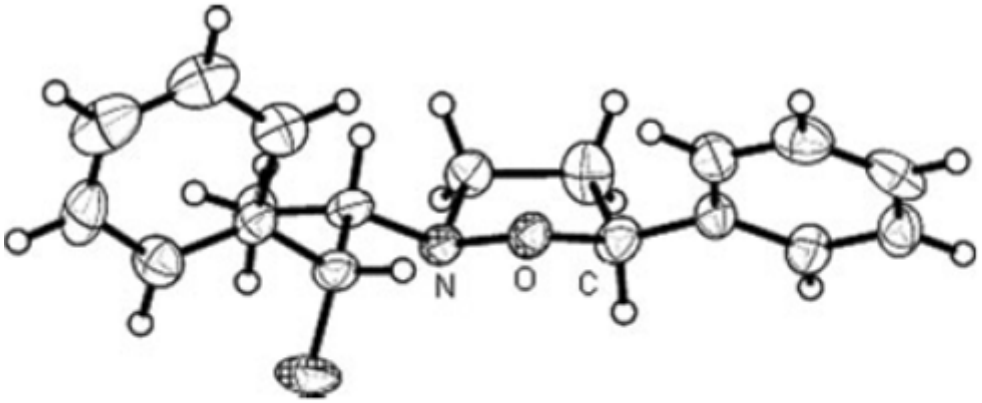


Figure molecular structure of **128b**. The Hydrogen atom of the hydroxyl group could not be located in difference-Fourier maps most probably due to disorder

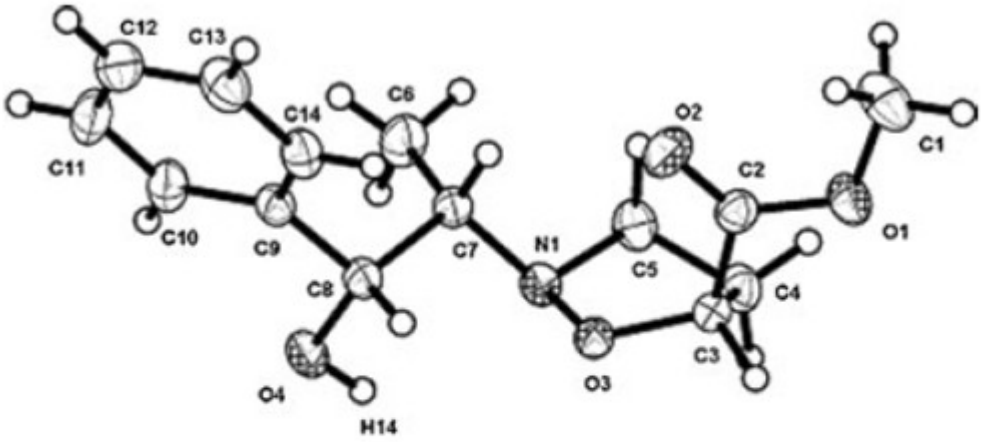
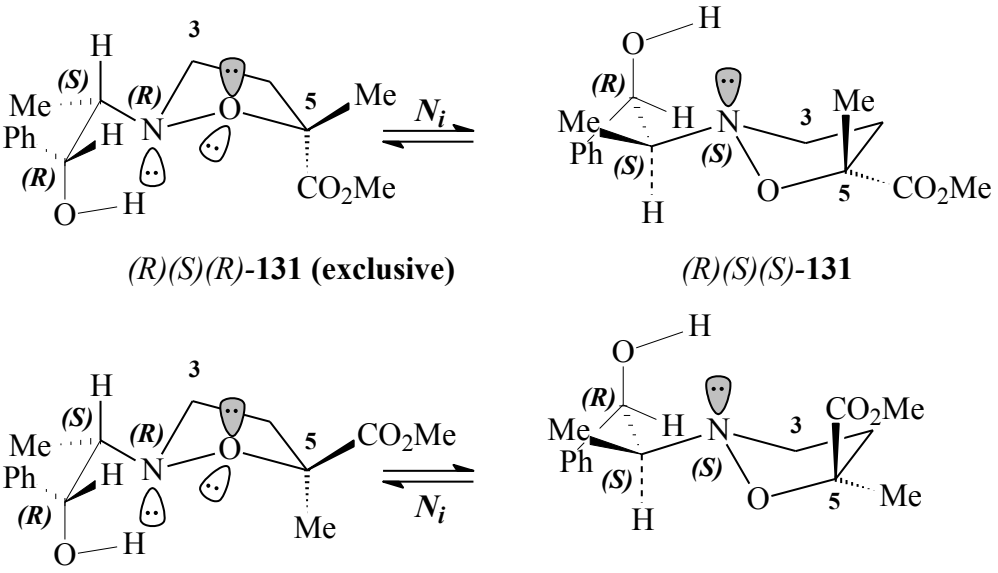


Figure 8. molecular structure **128c**

The question remains: why are the (R),(S),(R)-diastereomers more stable than their corresponding (R),(S),(S)-invertomers? It may be the result of an energetically favourable orientation of the groups around C-N having the larger substiuent (PhCHOH) in gauche

orientation with the ring 'O' in the major invertomer. The Newman projections also reveals that the 'OH' in the major invertomers is also capable of forming H-bond with the ring 'O', while this is not possible with the minor form. The special stability imparted by the (R),(S),(R) arrangement does not mind the substituent at C-5 to be trans or cis-oriented. Note that while the 2,5 substituents in **127(a-d)** remain trans oriented in the major invertomers, the cis remains the stable form for the corresponding isoxazolidines **128(a-d)**. The isoxazolidines **127c** and **127d** remained exclusively in the (R),(S),(R) configurations; the presence of the minor invertomers could not be detected. Presumably, the pseudoaxial orintantion of the CO_2Me is better tolerated in (R),(S),(R) invertomer for its smaller size as a result of the sp^2-hybridized carbon. It is worth mentioning that the C(5)-CH_2OH in the exclusive invertomer of **127d** may gain additional stability as a result of intramolecular H-bonding with the nitrogen as depicted in (Scheme 40).

The most interesting display of isomeric stability is found with the isoxazolidines **131**and **132**; while the former exists exclusively in the (R),(S),(R) form, the later remains in the (R),(S),(R) and R),(S),(S) forms in a respective ratio of 63:37 (Scheme 41, Table 3). The C(5)Me carbon of (R),(S),(R)-**7**, (R),(S),(S)-**131**, and (R),(S),(R)-**132** appeared at δ22.82, 22.95, and, 24.29 ppm, respectively; the similarity in the chemical shift values of the former two invertomers indicates the similar environments of the methyl group such as its *cis* orientation with the N(2) substituents. The extra stability enjoyed by the (R),(S),(R)-**131** invertomer could be attributed to the pseudoequatorial orientation of the bulkier substiutuents at C(5) and N(2), while the smaller CO_2Me is pseudoaxially-oriented.



(R)(S)(R)-**131 (exclusive)** *(R)(S)(S)*-**131**

(R)(S)(R)-**132 (major)** *(R)(S)(S)*-**132 (minor)**

Scheme 41.

The nitrogen inversion barrier is expected to be high when an oxygen atom is directly attached to the nitrogen as in isoxazolidines [83,84]. Experimental and calculated spectra for one of the ioxazolidines (**127b**) are shown in (Figure 8). The inversion barriers hover around 59 kJ/mol for most of the isoxazoldines (Table 3). The similar barriers were expected since the steric requirements to attain the sp^2 hybridized transition state (through which the nitrogen inversion occurs) remains more or less similar as the substituents in the immediate vicinity of nitrogen remains the same in all the isoxazolidines. An increase in the inversion barrier in in isoxaolidines in CD_3OD is attributed to the extra energy required for breaking of H-bonding prior to inversion [84]. However, the inversion in the current compounds in $CDCl_3$ also involves the breaking of the intramolecular H-bonding.

As a result the inversion barrier remains similar in hydrogen bonding solvent CD_3OD and non protic $CDCl_3$ for the compound **128c** (Table 3).

The solvent effects provided the additional support for the assigned stereochemistry. In methanol, the intramolecular H-bonding is disrupted; the steric bulk of the solvation shell of the nitrogen lone pair increases in hydrogen-bonding solvents. This should diminish the preference for the **127**-trans- and **128**-trans invertomers in CD_3OD since the steric bulk of the salvation lone pair salvation shell would interfere with the C(5) substituents (Scheme 3). This is exactly what is observed: the isoxazolidine *trans*-**127c** remained as the sole invertomer in $CDCl_3$ while in CD_3OD the **127**-*trans/cis* ratio becomes 83:17 (Table 3). For the isoxazolidine **128c** the trans/cis ratio of 21:79 in $CDCl_3$ is decreased to 13:87 in CD_3OD.

3.3 Experimental

3.3.1 General.

All m.p.s are uncorrected. I.r. spectra were recorded on a Perkin Elmer 16F PC FTi.r spectrometer. Elemental analysis was carried out on a EuroVector Elemental Analyzer Model EA3000. Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Paraformaldehyde, 1-hexene, styrene, allyl alcohol, methyl acrylate, methyl methacrylate, (-) norephedrine from Fluka were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. $MgBr_2$ was freshly prepared by reaction of Mg with 1,2-dibromoethane. All reactions were carried out under N_2.

The ^{13}C and variable temperature ^{1}H NMR spectra were recorded on a JEOL Lambda NMR spectrometer operating at 500.0 MHz. Most of the compounds were studied as 25 mg/cm^3 solutions in $CDCl_3$ and CD_3OD with TMS as internal standard. Multiplicities of the carbons were determined using DEPT experiments. X-ray crystallographic analysis was carried out on a Bruker-AXS Smart Apex system equipped with graphite-monochromatized Mo-Kα radiation (λ = 0.71073 Å). Optical rotaions were measured in a JASCO (P-2000) polarimeter. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N).

3.3.2 Hydroxylamine 126.

Chiral hydroxylamine **126** was prepared from (–) norephedrine in 38% yield using procedure as described [85]. The compound **126** was not fully characterized in the previous reports. M.p. 79-80°C (ether-hexane); $[\alpha]^{23}_{D}$ –26.3 (c 2.00, methanol). (Found: C, 64.5; H, 7.7; N, 8.3. $C_9H_{13}NO_2$ requires C, 64.65; H, 7.84; N, 8.38 %.);ν_{max} (KBr) 3480, 3270, 3239, 3081, 3055, 3025, 2974, 2933, 2897, 2877, 2795, 1488, 1442, 1380, 1350, 1314, 1243, 1200, 1140, 1092, 1070, 1049, 1034, 988, 942, 914, 890, 850, 736 and 691 cm^{-1}; δH($CDCl_3$, +25°C) : 0.85 (3H, d, J 6.7 Hz), 3.24 (1H, dq, J 2.8, 6.7 Hz), 5.17 (1H, d, J 2.8 Hz), 5.54 (2H, br, NHOH), 7.31 (5H, m); δC($CDCl_3$, +25°C) 10.25, 62.70, 71.93, 125.92 (2C), 127.21, 128.26 (2C), 141.37.

3.3.3 Nitrone 124.

Prepared via condensation of hydroxylamine **126** with paraformaldehyde, was not isolated (*vide infra*). But a crude ^{1}H NMR spectrum revealed the following signals

attributed to the nitrone: δH($CDCl_3$, +20°C) : 1.36 (3H, d, J 6.8 Hz), 4.10 (1H, m), 5.42 (1H, d, J 5.5 Hz), 6.38 (1H, d, J 7.1 Hz; CH=N), 6.54 (1H, d, J 7.1 Hz; CH=N), 7.35 (5H, m). However, the nitrone functionality accounted for only 20% of the product mixture as indicated by the integration of the olefinic protons of the nitrone functionalty versus the aromatic protons. The complicated spectra indicated the involvement of several compounds (e.g. **124-A**, **124-B**, *etc)* under equilibration with nitrone **124** as outlined in (Scheme 38).

3.3.4. Cycloaddition of nitrone 124 with 1-hexene (129a).

To a solution of hydroxylamine **126** (670 mg, 4.0 mmol) in toluene (10 cm^3) was added paraformaldehyde (200 mg, 6.7 mmol) and 1-hexene (3 cm^3). The mixture was stirred using a magnetic stir bar in the closed vessel under N_2 at 105°C for 12 h. After removal of the solvent the residual mixture was chromatographed over silica using ether/hexane mixture as eluant to give pure isomer **127a** followed by a mixture of the adducts **127a** and **128a** as a colourless liquid. The combined yield of the cycloadducts was found to be 89%. Spectral analysis adducts revealed the presence of **127a**/**128a** in a ratio of 50:50, respectively, as determined by integration and peak heights of C(5)H signals.

127a: $[\alpha]^{23}_D$ −8.5 (c 0.946, methanol); m/z 156 [M^+-107 (PhCHOH)]; (Found: C, 72.8; H, 9.5 ; N, 5.2. $C_{16}H_{25}NO_2$ requires C, 72.97; H, 9.57; N, 5.32 %.); ν_{max} (neat) 3517, 3214, 3061, 3027, 2956, 2930, 2859, 1495, 1451, 1379, 1332, 1231, 1198, 1097, 1067, 999, 878, 750 and 702 cm^{-1}; δH($CDCl_3$, +20°C) : 0.81 (3H, m), 0.91 (3H, t, J 7.0 Hz) 1.15-2.00 (7H, m), 2.36 (1H, m), 2.50-3.50 (4H, m), 4.13 (1H, m), 5.20 (1H, apparent s), 7.30 (5H, m).

The ^{1}H NMR spectrum in $CDCl_3$ at -40°C revealed the presence of two invertomers in a 83:17 ratio as determined by integration of several proton signals.

Major invertomer: δH($CDCl_3$, -40°C) : 0.81 (3H, d, J 6.4 Hz), 0.92 (3H, t, J 7.0 Hz) 1.15-1.55 (5H, m), 1.72 (1H, m), 1.93 (1H, m), 2.39 (1H, m), 2.83 (1H, m), 2.90 (1H, m), 3.26 (1H, m), 3.98 (1H, br , OH), 4.20 (1H, quint, J 6.3 Hz), 5.26 (1H, d, J 3.0 Hz), 7.35 (5H, m); δC($CDCl_3$, -40°C) 10.88, 14.26, 22.72, 28.42, 33.90, 35.13, 52.32, 65.68, 72.59, 76.75, 125.96 (2C), 126.73, 127.89 (2C), 140.94.

Minor invertomer: The minor invertomer has the follwing non-overlapping signals: δH($CDCl_3$, -40°C) 1.00 (3H, d, J 6.5 Hz), 3.05 (1H, m), 3.51 (1H, m), 4.05 (1H, quint, J 6.9 Hz), 5.14 (1H, d, J 5.2 Hz); δC($CDCl_3$, -40°C) 7.12, 14.21, 22.77, 28.24, 33.81, 34.23, 52.06, 67.26, 74.81, 77.50, 125.71 (2C), 126.84, 127.99 (2C), 141.24.

128a: The second fraction was contaminated with a minor amount of **127a**. The following signals were attributed to **128a**. The ^{1}H NMR spectrum in $CDCl_3$ at -40°C revealed the presence of two invertomers in a 89:11 ratio as determined by integration of benzylic proton signals. (Found: C, 72.7; H, 9.4 ; N, 5.2. $C_{16}H_{25}NO_2$ requires C, 72.97; H, 9.57; N, 5.32 %.); m/z 156 [M^{+}-107 (PhCHOH)]; ν_{max} (neat) 3424, 3062, 3027, 2958, 2929, 2858, 1494, 1452,1379, 1336, 1197, 1097, 1020, 999, 911, 751, 731 and 702 cm^{-1}.

Major invertomer: δH($CDCl_3$, -40°C) : 0.81 (3H, d, J 6.3 Hz), 0.87 (3H, t, J 6.7 Hz), 1.15-2.00 (7H, m), 2.40 (1H, m), 2.60 (1H, m), 2.91 (1H, m), 3.33 (1H, m), 4.05 (1H, m), 4.22 (1H, br , OH), 5.35 (1H, d, J 2.5 Hz), 7.35 (5H, m); δC($CDCl_3$, -40°C) 10.75, 14.25,

22.82, 28.26, 33.61, 34.56, 53.13, 68.02, 72.31, 77.48, 126.15 (2C), 126.69, 127.87 (2C), 141.22.

Minor invertomer: The minor invertomer has the following non-overlapping signals: δH($CDCl_3$, -40°C) 5.00 (1H, d, J 5.0 Hz). δC($CDCl_3$, -40°C) 7.42, 12.54, 22.72, 28.40, 33.83, 34.24, 51.87, 65.93, 73.96, 74.38, 125.63 (2C), 126.95, 128.25 (2C), 141.00.

3.3.5. Cycloaddition of nitrone 124 with styrene (129b).

To a solution of the hydroxylamine **126** (670 mg, 4.0 mmol) in toluene (10 cm^3) was added paraformaldehyde (200 mg, 6.7 mmol) and styrene (3 cm^3). The mixture was stirred using a magnetic stir bar in the closed vessel under N_2 at 90°C for 6 h. After removal of the solvent and excess styrene the residual mixture was chromatographed over silica using 9:1 ether/hexane mixture as eluant to give pure isomer **127b** followed by a mixture of the adducts **127b** and **128b**. Continued elution afforded the pure adduct **127b**. The combined yield of the cycloadducts was found to be 89%. Spectral analysis adducts revealed the presence of **127**/**128** in a ratio of 40:60, respectively, as determined by integration of several non overlapping signals of the C(5)H and Me doublets.

Minor isomer **127b**: Mp 65-66°C (ether-pentane); m/z 176 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ +37.1 (c 0.488, methanol). (Found: C, 76.1; H, 7.5; N, 4.8. $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94 %.);ν_{max} (KBr) 3423, 3081, 3055, 3025, 2984, 2948, 2897, 2831, 1595, 1488, 1447, 1437, 1380, 1334, 1299, 1278, 1197, 1105, 1094. 1023, 1013, 916, 885, 854, 798, 752 and 696 cm^{-1}.

The ^{1}H NMR spectrum in $CDCl_3$ at -40°C revealed the presence of two invertomers in a 88:12 ratio as determined by integration of several proton signals.

Major invertomer: δH($CDCl_3$, -40°C) : 0.85 (3H, d, J 6.4 Hz), 2.38 (1H, m), 2.82 (1H, m), 2.96 (2H, m), 3.44 (1H, m), 3.62 (1H, OH), 5.27 (1H, apparent t, J 7.2 Hz), 5.43 (1H, s), 7.35 (10H, m); δC($CDCl_3$, -40°C) 10.73, 37.48, 53.02, 66.31, 72.44, 77.57, 125.67 (2C), 125.88 (2C), 126.81, 127.48, 127.99 (2C), 128.54(2C), 140.71, 142.57.

Minor invertomer: The minor invertomer has the following non-overlapping signals: δH($CDCl_3$, -40°C) 1.09 (3H, d, J 6.4 Hz), 3.18 (1H, m), 3.70 (1H, m), 5.07 (1H, apparent t, J 7.2 Hz), 5.22 (1H, s); δC($CDCl_3$, -40°C) 6.44, 36.97, 52.38, 66.71, 75.68, 78.95, 125.75 (2C), 126.60 (2C), 126.75, 127.00, 128.05 (2C), 128.44 (2C), 140.34, 141.01.

Major isomer **128b**: Mp 74-75°C (ether-pentane); m/z 176 [M^{+}-107 (PhCHOH)]; $[\alpha]^{23}_{D}$ −17.8 (c 0.386, methanol); (Found: C, 76.2; H, 7.3; N, 5.0. $C_{18}H_{21}NO_2$ requires C, 76.30; H, 7.47; N, 4.94 %.);ν_{max} (KBr) 3375, 3029, 2980, 2937, 2851, 1603, 1493, 1450, 1381, 1367, 1341, 1327, 1284, 1241, 1204, 1156, 1096, 1043, 1001, 944, 919, 880, 823, 753 and 699 cm^{-1}.

The ^{1}H NMR spectrum in CDCl3 at -40°C revealed the presence of two invertomers in a 87:13 ratio as determined by integration of Me doublets.

Major invertomer: δH($CDCl_3$, -40°C) 0.94 (3H, d, J 6.7 Hz), 2.15 (1H, m), 2.74 (2H, m), 3.02 (1H, m), 3.47 (1H, m), 4.49 (1H, s, OH), 5.06 (1H, m), 5.43 (1H, s), 7.35 (10H, m);

δC($CDCl_3$, -40°C) 10.65, 36.93, 53.90, 68.15, 71.98, 78.77, 125.99 (2C), 126.69, 126.76 (2C), 127.88, 127.93 (2C), 128.39 (2C), 140.79, 141.44.

Minor invertomer: The minor invertomer has the following non-overlapping signals: δH($CDCl_3$, -40°C) 1.02 (3H, d, J 6.5 Hz). δC($CDCl_3$, -40°C) 7.45, 37.51, 52.54, 65.99, 74.70, 78.85, 125.68 (2C), 125.88, 126.08 (2C), 127.05, 128.09 (2C), 128.52 (2C), 140.79, 141.44.

3.3.6 Cycloaddition of nitrone 124 with methyl acrylate (129c).

A mixture of the hydroxylamine **126** (670 mg, 4.0 mmol) and paraformaldehyde (200 mg, 6.7 mmol) in chloroform (15 cm^3) was stirred using a magnetic stir bar in a closed vessel under N_2 at 65°C for 2 h. Methyl acrylate (2 cm^3) was then added to the resulting nitrone solution (at 25°C) and stirring was continued at 60°C for 24 h. After removal of the solvent and excess alkene, the residual mixture was chromatographed over silica using 9:1 hexane/ether mixture as eluant to give the minor isomer **127c** (417 mg). Continued elution afforded the pure sample of the major isomer **128c** (580 mg). Adducts **127c** and **128c** were thus formed in a ratio of 42:58, respectively. The ^{1}H NMR analysis of the crude cycloadducts also supported the ratio obtained from the chromatographic separation. The combined yield of the cycloadducts was found to be 94%.

Minor isomer **127c**: Mp 68-69°C (ether-pentane); m/z 158 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ –48.3 (c 0.425, methanol); (Found: C, 63.2; H, 7.1; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28 %.); ν_{max} (KBr) 3485 (sharp), 3061, 2986, 2958, 2847, 1746, 1496, 1451, 1430, 1380, 1337, 1286, 1205, 1177, 1086, 1026, 1003, 812, 752 and 705 cm^{-1}.

Sharp ^{1}H NMR signals at room temperature indicated the presence of a single invertomer: δH($CDCl_3$, +25°C) : 0.78 (3H, d, J 6.7 Hz), 2.48-2.70 (3H, m), 2.92 (1H, m), 3.32 (1H, m), 3.57 (1H, s , OH), 3.80 (3H,s), 4.63 (1H, dd, J 3.9, 9.7 Hz), 5.38 (1H, s), 7.33 (5H, m). The spectrum at -40°C remained similar to that at +25°C. δC($CDCl_3$, -40°C) 11.07, 32.90, 51.63, 52.73 (OMe), 65.79, 72.03, 73.38, 125.69 (2C), 126.80, 128.01 (2C), 140.25, 173.87.

In CD_3OD (-40°C) the ^{1}H NMR spectrum revealed several nonoverlapping minor signals indicating the major/minor invertomers of **127c** in a ratio of 83:17. The CH_3 doublets appeared at δ0.77 (major, d, J = 6.7 Hz) and δ1.02 (minor, d, J = 6.1 Hz). The benzylic proton appeared at δ5.38 (major, s) and δ5.17 (minor, s).

Major isomer **128c**: Mp 60-61°C (ether-pentane);); m/z 158 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ –26.4 (c 0.872, methanol); (Found: C, 63.3; H, 7.1; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28 %.); ν_{max} (KBr) 3543 (sharp), 3081, 2990, 2942, 2908, 2869, 1754, 1492, 1453, 1434, 1409, 1378, 1349, 1328, 1284, 1262, 1198, 1088, 1061, 996, 964, 949, 877, 854, 795, 763 and 706 cm^{-1}.

The ^{1}H NMR spectrum in $CDCl_3$ at -40°C revealed the presence of two invertomers in a 79:21 ratio as determined by integration of several proton signals.

Major invertomer: δH($CDCl_3$, -40°C) : 0.84 (3H, d, J 6.7 Hz), 2.39 (1H, m), 2.66 (1H, m), 2.89 (1H, m), 3.11 (1H, m), 3.31 (1H, m), 3.75 (1H, s , OH), 3.83 (3H, s), 4.64 (1H, dd, J 5.8, 9.2 Hz), 5.45 (1H, s), 7.37 (5H, m); δC($CDCl_3$, -40°C) 10.48, 32.98,

51.78, 52.67 (OMe), 66.92, 71.68, 75.09, 125.84 (2C), 126.70, 127.95 (2C), 141.09, 172.47.

Minor invertomer: The non overlapping ^{1}H signals at δH($CDCl_3$, -40°C) 0.95 (3H, d, J 6.7 Hz), 5.18 (1H, s); δC($CDCl_3$, -40°C) 5.14, 32.18, 50.59, 52.79 (OMe), 64.46, 74.05, 76.20, 125.66 (2C), 127.00, 128.06 (2C), 140.57, 173.33.

In CD_3OD (-40°C) the ^{1}H NMR spectrum revealed several nonoverlapping minor signals indicating the major/minor invertomers of **128c** in a ratio of 87:13. The CH_3 doublets appeared at δ0.80 (major, d, J = 6.7 Hz) and δ1.01 (minor, d, J = 6.1 Hz). The benzyl protons appeared at δ5.47 (major, s) and δ5.17 (minor, s).

3.3.7. Lithium aluminium hydride reduction of cycloadducts methyl acrylate adducts (127c, 128c) to allyl alcohol adducts (127d, 128d).

127d: To a stirred solution of **127c** (120 mg, 0.45 mmol) in ether (15 cm^3) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1 g) and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using a 95:5 CH_2Cl_2/methanol as the eluant to give **127d** as a colorless liquid (100 mg, 94%), $[\alpha]^{23}_D$ –38.7 (c 1.53, methanol); m/z 130 [M^+-107 (PhCHOH)]; (Found: C, 65.6; H, 7.8; N, 5.7. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90 %.); ν_{max}.

(neat) 3402, 3060, 3027, 2981, 2940, 1494, 1450, 1380, 1334, 1236, 1199, 1097, 1041, 993, 859, 807, 736 and 703 cm^{-1}.

Sharp ^1H NMR signals at room temperature indicated the presence of a single invertomer. The spectrum at -40°C remained similar to that at +25°C.

Single invertomer: δH($CDCl_3$, -40°C) 0.85 (3H, d, J 6.4 Hz), 2.13 (1H, m), 2.30 (1H, m), 2.72 (1H, m), 2.81 (1H, m), 3.22 (1H, m), 3.72 (2H, m), 4.37 (1H, m), 4.75 (1H, broad, OH), 4.89 (1H, broad, OH), 5.43 (1H, s), 7.35 (5H, m). δC ($CDCl_3$, -40°C) 10.36, 29.44, 53.03, 63.60, 67.30, 71.71, 77.47, 125.86 (2C), 126.73, 127.94 (2C), 141.40.

128d: Adduct **128c** was reduced with $LiAlH_4$ using procedure as described above to give **128d** (95%) as a colorless liquid; $[\alpha]^{23}_D$ −18.4 (c 1.58, methanol); m/z 130 [M^+-107 (PhCHOH)]; (Found: C, 65.5; H, 7.9; N, 5.8. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); ν_{max}. (neat) 3286, 2982, 2880, 1494, 1451, 1381, 1336, 1198, 1041, 999, 887, 829, 751 and 703 cm^{-1}.

The ^1H NMR spectrum in $CDCl_3$ at -40°C revealed the presence of two invertomers in a 84:16 ratio as determined by integration of several proton signals.

Major invertomer: δH($CDCl_3$, -40°C) 0.88 (3H, d, J 6.7 Hz), 1.85 (1H, m), 2.33 (1H, m), 2.44 (1H, m), 2.87 (1H, m), 3.37 (1H, m), 3.64 (1H, m), 3.81 (1H, m), 4.41 (2H, m, including an OH), 4.87 (1H, broad s, OH), 5.42 (1H, s), 7.35 (5H, m); δC($CDCl_3$, -40°C) 10.62, 30.03, 53.64, 64.29, 67.98, 71.61, 77.67, 125.99 (2C), 126.71, 127.91 (2C), 141.08.

Minor invertomer: The minor invertomer has the non overlapping ^{1}H signals at: δH($CDCl_3$, -40°C) 1.00 (3H, d, J 6.4 Hz), 5.02 (1H, s); δC($CDCl_3$, -40°C) 7.37, 29.26, 52.26, 63.84, 66.09, 74.72, 78.07, 125.67 (2C), 127.13, 128.09 (2C), 140.85.

3.3.8. Cycloaddition of nitrone 124 with allyl alcohol (129d).

To a solution of the hydroxylamine **126** (670 mg, 4.0 mmol) in toluene (10 cm^3) was added paraformaldehyde (200 mg, 6.7 mmol) and allyl alcohol (3 cm^3). The mixture was stirred using a magnetic stir bar in the closed vessel under N_2 at 90°C for 12 h. After removal of the solvent the residual mixture was chromatographed over silica using 98:2 dicholromethane/methanol mixture as eluant to give a non separable mixture of adducts **127d** and **128d** as a colourless liquid (0.80 g, 84%). Spectral analysis revealed the presence of **127d**/**128d** in a ratio of 50:50.

3.3.9. Cycloaddition of nitrone 124 with allyl alcohol (129d) in the presence of MgBr2.

To a solution of hydroxylamine **126** (167 mg, 1.0 mmol) in dichloromethane (20 cm^3), was added paraformaldehyde (34 mg, 1.13 mmol) and the mixture was stirred in a closed vessel under N_2 at 65°C for 2 h. Thereafter, the solution was cooled to room temperature and the volume of the solution was reduced to 5 cm^3 by gently blowing N_2 at 40°C. This process is expected to remove moisture (H_2O) by evaporation along with CH_2Cl_2. Then $MgBr_2$ (184 mg, 1.0 mmol) was added to the solution. The resulting suspension was stirred at 20°C for 15 min after which allyl alcohol (**129d**) (4.0 mmol) was added. The reaction mixture was then stirred at 65°C in the closed vessel under N_2 for 48 h. After the elapsed time, the reaction mixture was cooled to room temperature and was

taken up in 10% K_2CO_3 (20 cm^3) and extracted with CH_2Cl_2 (3 × 20 cm^3). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography using 98:2 dichloromethane/methanol mixture as eluent to give a non-separable mixture of isomers **127d** and **128d** as a colourless liquid (190 mg, 80%). The ratio of **127d** and **128d** was found to be 50:50, respectively, as determined by ^{1}H NMR spectroscopic analysis (*vide supra*). The Lewis acid catalyzed **129a-c** cycloaddition thus failed to improve the diastereselectivity of the addition reaction.

3.3.10. Cycloaddition of nitrone 124 with methyl methacrylate (130).

A mixture of the hydroxylamine **126** (670 mg, 4.0 mmol) and paraformaldehyde (200 mg, 6.7 mmol) in chloroform (15 cm^3) was stirred using a magnetic stir bar in the closed vessel under N_2 at 65°C in a closed vessel for 2 h. Methyl methacrylate (**130**) (2 cm^3) was then added to the resulting nitrone solution (at 25°C) and stirring was continued at 60°C for 24 h. After removal of the solvent and excess alkene, the residual mixture was chromatographed over silica using 9:1 hexane/ether mixture as eluant to give the minor isomer **131** (371 mg). Continued elution afforded the pure sample of the major isomer **132** (690 mg). Adducts **131** and **132** were thus formed in a ratio of 35:65, respectively. The ^{1}H NMR integration of the benzylic proton signals ($CDCl_3$, +25°C) of the crude cycloadducts at δ 5.39 (minor) and 5.26 (major) also supported the ratio obtained from the chromatographic separation. The combined yield of the cycloadducts was found to be 95%.

131: Single invertomer: Mp 78-79°C (ether-pentane); m/z 172 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ −70.8 (c 0.267, methanol). (Found: C, 64.3; H, 7.4; N, 4.9.

$C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01 %.); ν_{max} (KBr) 3502 (very sharp), 3059, 2994, 2955, 2882, 2840, 1738, 1499, 1449, 1409, 1383, 1341, 1279, 1232, 1201, 1126, 1070, 1023, 1002, 971, 933, 906, 848, 818, 752 and 706 cm^{-1}; δH($CDCl_3$, +25°C) : 0.73 (3H, d, J 6.7 Hz), 1.56 (3H, s), 2.13 (1H, ddd, J 2.1, 9.1 12.7 Hz), 2.60 (1H, m), 2.84 (1H, td, J 8.7, 12.6 Hz), 2.91 (1H, dq, J 2.9, 6.6 Hz), 3.29 (1H, dt, J 2.1, 8.7 Hz), 3.58 (1H, s , OH), 3.80 (3H,s), 5.39 (1H, br s), 7.33 (5H, m). Identical ^{1}H NMR spectrum was obtained at -40°C. δC($CDCl_3$, -40°C) 10.80, 22.82, 39.13, 52.50, 52.89 (OMe), 65.81, 71.90, 81.11, 125.70 (2C), 126.73, 127.96 (2C), 140.31, 176.31.

132: Mp 49-50°C (ether-pentane); m/z 172 [M^+-107 (PhCHOH)]; $[\alpha]^{23}_D$ +13.5 (c 0.942, methanol); (Found: C, 64.4; H, 7.6; N, 4.9. $C_{15}H_{21}NO_4$ requires C, 64.50; H, 7.58; N, 5.01 %.); ν_{max} (KBr) 3408, 2999, 2948, 2854, 1741, 1495, 1450, 1383, 1316, 1278, 1203, 1147, 1099, 1064, 1032, 988, 926, 871, 756 and 705 cm^{-1}.

The 1H NMR spectrum in CDCl3 at -40°C revealed the presence of two invertomers in a 63:37 ratio as determined by integration of several proton signals.

Major invertomer: δH($CDCl_3$, -40°C) : 0.80 (3H, d, J 6.7 Hz), 1.57 (3H, s), 2.26 (1H, m), 2.71 (1H, m), 2.83-3.25 (2H, m), 3.34 (1H, m), 3.67 (1H, s , OH), 3.84 (3H, s), 5.39 (1H, s), 7.37 (5H, m); δC($CDCl_3$, -40°C) 10.55, 24.29, 39.02, 52.08, 52.94 (OMe), 66.31, 72.06, 82.17, 125.82 (2C), 126.69, 127.92 (2C), 141.04, 174.73.

Minor invertomer: The invertomer has the following non overlapping 1H signals at δH($CDCl_3$, -40°C) 0.94 (3H, d, J 6.7 Hz), 2.11 (1H, m), 1.55 (3H, s), 3.98 (1H, s, OH),

5.21 (1H, s); δC($CDCl_3$, -40°C) 4.00, 22.95, 38.10, 51.06, 52.90 (OMe), 64.06, 76.91, 81.63, 125.60 (2C), 126.90, 128.04 (2C), 140.64, 176.01.

Inversion barrier calculations. Simulations of exchange-affected proton spectra for all compounds were carried out using a computer program AXEX[86], corresponding to a two non coupled sites exchange with unequal populations. The following signals were utilized: **127a** (or **128a**), benzyl protons at δ5.26 (major, s) and δ5.14 (minor, s); **128a** (or **127a**), benzyl protons at δ5.35 (major, s) and δ5.00 (minor, s); **127b**: ($CDCl_3$), CH_3 doublets appeared at δ0.85 (major) and δ1.09 (minor); **128b**: ($CDCl_3$), CH_3 doublets appeared at δ0.94 (major) and δ1.02 (minor); **127c**: (CD3OD), CH3 doublets appeared at δ0.77 (major) and δ1.02 (minor); **128c**: ($CDCl_3$), benzyl protons at δ5.45 (major, s) and δ5.18 (minor, s); **128c**: (CD_3OD), methyl doublets at δ0.80 (major) and δ1.01 (minor); **128d**: ($CDCl_3$), benzyl protons at δ5.42 (major, s) and δ5.02 (minor, s); **132**: ($CDCl_3$), benzyl protons at δ5.39 (major, s) and δ5.21 (minor, s).

Simulations of exchange affected triplets were carried out by modifying the two-site exchange program [87]. The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange. Simulations of exchange affected doublet of doublets were carried out by modifying the two-site exchange program.12 The first order coupling to these protons is simply assumed as giving overlapping two site exchanges with the same population ratio and equal rates of exchange.

CHAPTER 4

Peracid induced ring opening of some hexahydro-2H-isoxazol [2, 3-a] pyridines to second-generation cyclic aldonitrones

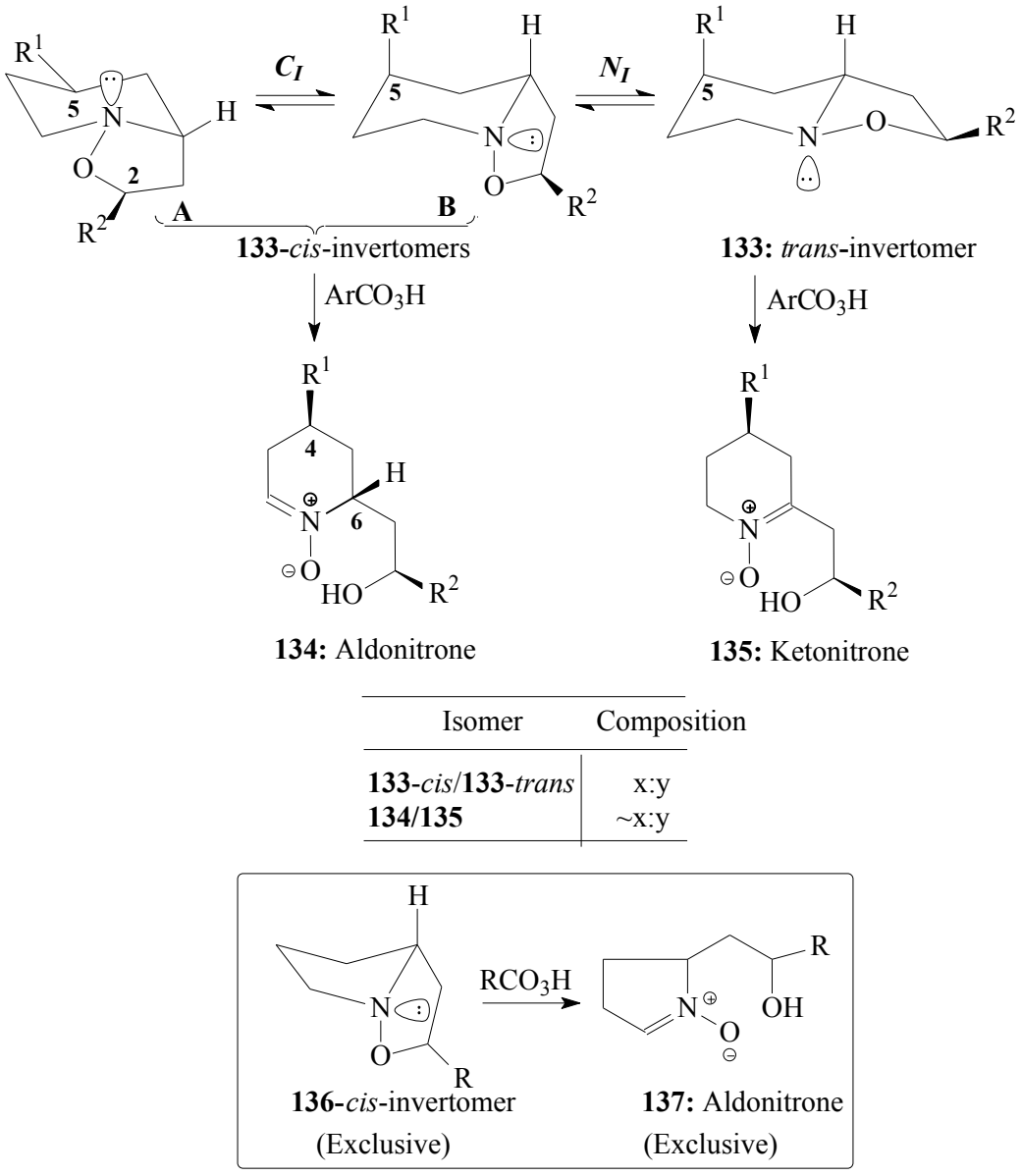
Summary:

A study of the stereo- and face-selectivity of the cycloaddition reactions of several mono- and disubstituted alkenes with 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide has been carried out. The addition reactions have displayed a very high degree of face selectivity (13-48:1). Use of dimethyl methylenemalonate as a protective group in nitrone cycloaddition reactions has been demonstrated. The invertomeric analysis revealed that the bicyclic cycloadducts remain predominantly as the cis-fused isomer which leads to the formation of synthetically important second-generation cyclic aldonitrones via peracid oxidation. One interesting finding was that treatment of the cycloadducts with two equivalents of peracid afforded the cyclic N-hydroxy lactams, presumably via further oxidation of the aldonitrones. The piperidine ring has been elaborated by cycloaddition reaction of the second-generation nitrones with several alkenes, which in most cases gave the cycloadducts in a stereoselective manner.

4.1 Introduction

1,3-Dipolar cycloaddition reaction of nitrones with alkenes has become an important tool in the synthesis of natural products [2]. The efficacy of these additions lies on the remarkable selectivity in the incorporation of multiple stereocenters in a single step [2]. The cyclic nitrones have been shown to exhibit greater stereoselectivity and reactivity compared to their acyclic counterparts as a result of the former existing in the E

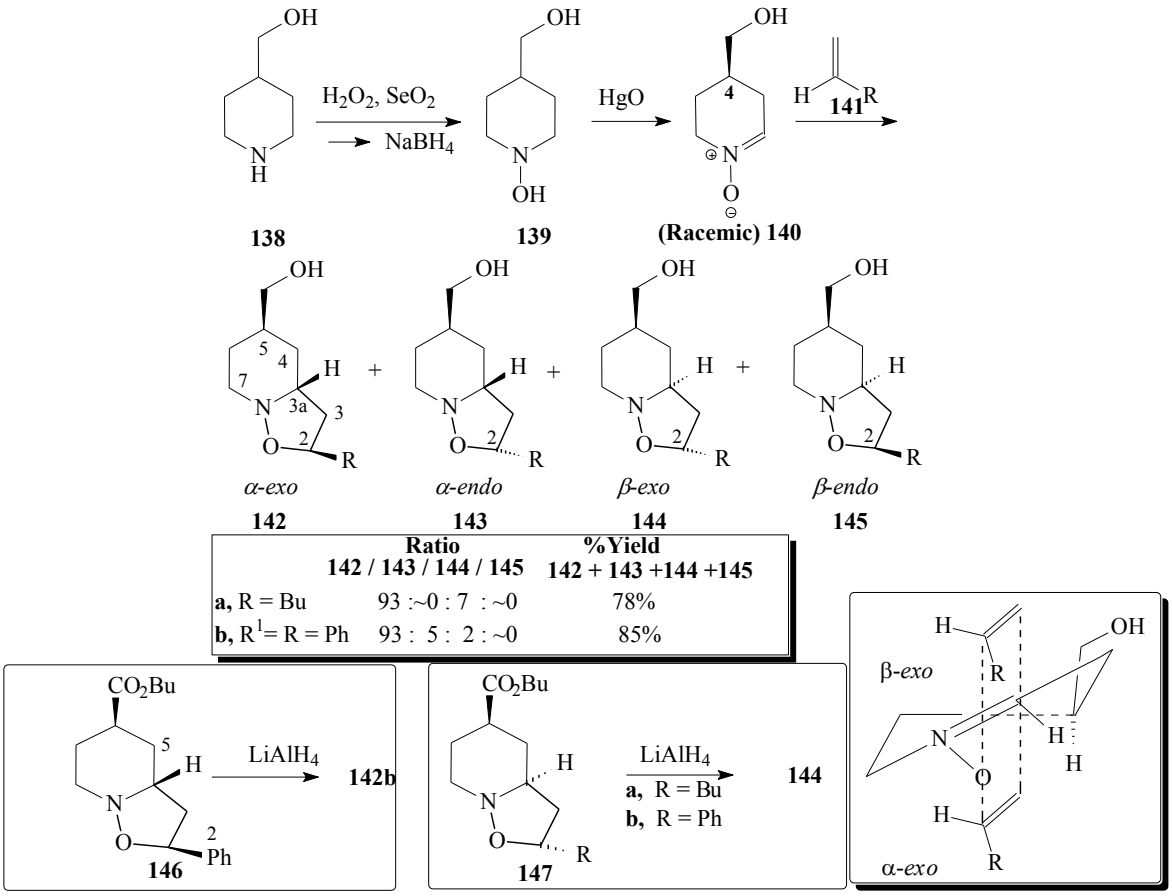
form [2,88]. The pyrrolidine- and piperidine-based alkaloids, which are widespread in nature, can be accessed through the cycloaddition reaction of five- and six-membered cyclic nitrones, respectively [2]. Nitrones generated by peracid-induced ring opening of the cycloaddition products derived from cyclic nitrones marked the beginning of the utilization of the second-generation of cyclic nitrones (Scheme 40) [89]. However, the proper utilization of these second-generation nitrones has been hampered by the lack of selectivity [90] in the oxidation process in the 6/5-fused isoxazolidines **133** (R1=H), where the major or sole trans invertomer leads to the synthetically less important ketonitrone **135** either as the major or sole product. Orientation of the nitrogen lone pair, and the *trans/cis* invertomer ratio dictate the regiochemical outcome of the oxidation process. The higher activation barrier to nitrogen inversion mett principle [91] to apply; as such the *trans* and cis invertomers in a ratio of x:y afford ($\Delta G^{\#}$, ~70 kJ/mol)6b than the oxidation process does not permit the Curtin-Ham the keto- and aldo-nitrones, respectively, in a similar ratio. However, the corresponding 5/5-fused isoxazolidines **136**, which exist only as the *cis*-invertomers, give aldonitrones **137** exclusively (Scheme 42) [72].



Scheme 42.

Note that the 6/5-fused isoxazolidines **133** (R1=H) remain in the *trans*-form as the major or sole invertomer (Scheme 42). In our continuing efforts to generate the synthetically important aldonitrones **134** in grater proportions, we realized that the proportion of the *cis*-invertomer has to be increased at the expense of its *trans* counterpart. Attachment of an ester functionality (R1 = CO_2R) *via* its sp^2 hybridized carbon at C(5) in

133 did bring about a moderate change in the composition favouring the *cis* invertomer A as a result of the equatorially-oriented CO_2R group [73] We anticipated that a C(5) substituent attached through a sp^3 hybridized carbon (having a larger steric size than its sp^2 counterpart) would motivate the ring further in the direction of the *cis*-invertomer A. Hence we report, for the first time, the face- and stereo-selectivity of cycloaddition of a new cyclic nitrone **140** (Scheme 43) having a hydroxymethyl substituent at C(4) with various alkenes. The invertomer analysis and peracid-induced ring opening of the resultant cycloadducts may lead to the second-generation cyclic aldonitrones (Scheme 42) more selectively. The study would give an opportunity to examine the face selectivity associated with cycloaddition of the second-generation nitrones 4,6-disubstitued-3,4,5,6-tetrahydropyridine 1-oxides **134**.



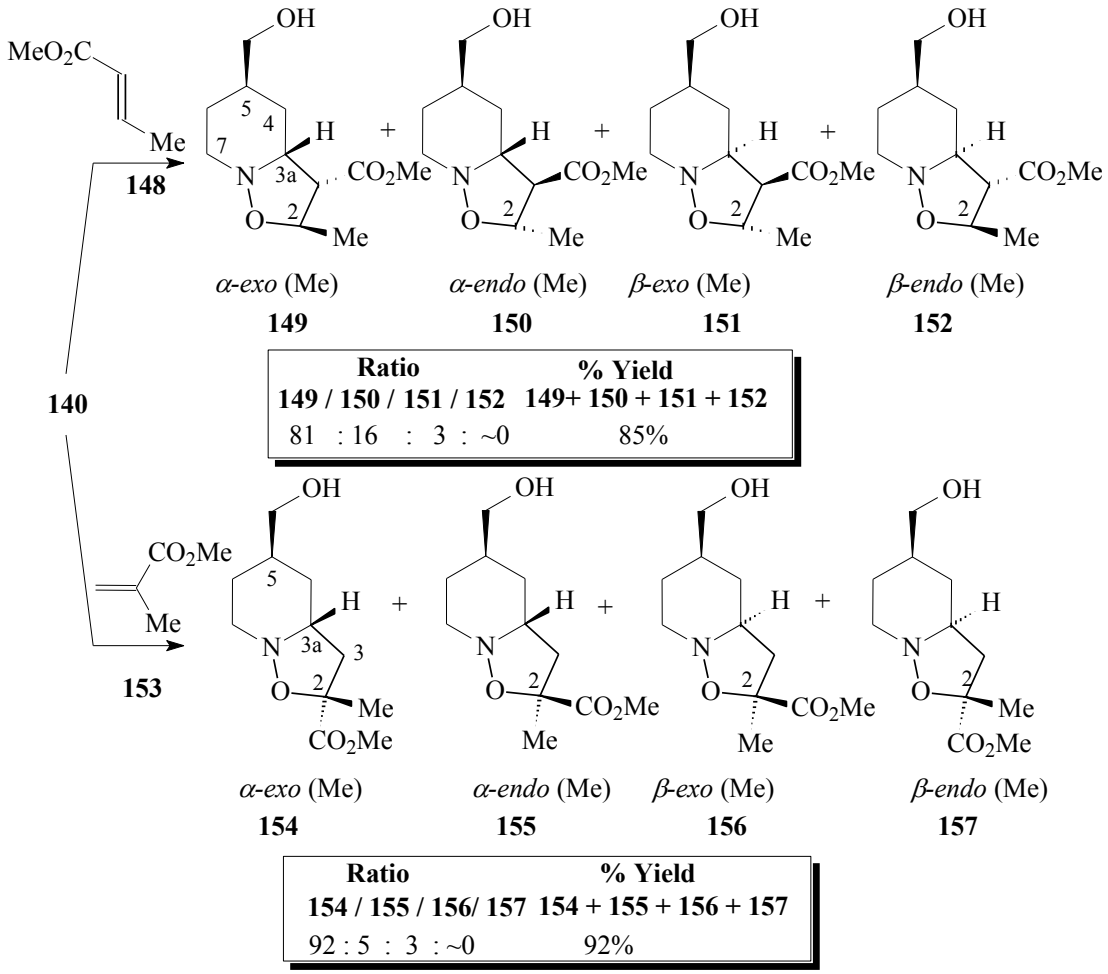
Scheme 43.

4.2 Results and Discussion

The synthesis of nitrone **140** is outlined in (Scheme 43). It was presumed at the outset that preparation of the nitrone by direct oxidation of the secondary amine **138** will be a trivial matter. However, we were unable to obtain the nitrone by the procedure of Murahashi *et al*.[92] using hydrogen peroxide oxidation mediated by selenium dioxide either in acetone or methanol. The oxidation process gave a complicated mixture of products (presumably a mixture of **139**, **140**, and other products), which upon treatment with $NaBH_4$ afforded the hydroxylamine **139**. The required nitrone **140** was then prepared by mercury(II) oxide oxidation of **139** (Scheme 43).

Next, we pursued the addition reaction of nitrone **140** with various alkenes. The addition of monosubstituted alkene 1-hexene (**141a**) was found to be stereo-, as well as highly face-selective; a mixture of diasteromers **142a** and **144a** was obtained in a ~13:1 ratio. The configuration of the major adduct **142a** was based on the sterically favourable exo approach (Scheme 43) of the Bu group from the less hindered face (i.e. α face) of the nitrone, while the β-*exo* approach of the alkene afforded the adduct **144a**. We are unable to detect the formation of the stereoisomers **143a** and **145a** arising from the α-endo and β-endo mode of approach, respectively, by the alkene. Likewise, the addition reaction with styrene (**141b**) led to the formation of the cycloadducts **142b**-**145b** in a ratio of 93:5:2:~0, thereby ascertaining again the highly face selective (98:2) nature of the cycloadditions. Such a high selectivity is surprising since the C(4)-CH_2OH group imparting the facial difference is positioned at the furthest point from the nitrone functionality in **140**. The face selectivitiy of the nitrone **140** was found to be better than a nitrone containing C(4)-CO_2Bu group (attached to the ring through a sp^2 carbon) [73]. In order to confirm the stereochemistry of the cycloadducts, the compounds **146**, **147a**, and **147b** having known configurations [73] , were converted into **142b**, **144a** and **144b**, respectively (Scheme 43).

The addition of disubstituted alkenes methyl crotonate (**148**) and methyl methacrylate (**153**) to the nitrone **140** also demonstrated very high face selectivity (97:3) in each case (Scheme 44). In both cases, the major adducts (i.e. **149** and **154**) were obtained *via* α-*exo* (Me) approach. The stereochemistry is based on the precedent in the lietrature [73,18] - the major adducts were obtained *via* an *endo*-oriented methoxycarbonyl group in the transition state as a result of a favourable secondary orbital interaction.



Scheme 44.

In order to study the effect of increasing the steric bulk of the C(4) substitituent in nitrone **140**, the nitrone was first protected by reacting with dimethyl methylenemalonate (**158**) to give a regioisomeric mixture of **159a** and **160a** which upon silylation afforded **159b** and **160b** (Scheme 45). Similar electronic controlled reversal in the regioselections are known [72] in the addition reaction of the highly electron deficient alkene **158**. The nitrone functionality is protected in the sense that the cycloadducts derived from the highly electron deficient alkene readily undergo cycloreversion to the starting reactants [72].

Thus upon thermolysis at 90°C, either **159b** or **160b** was changed to a mixture of **159b** and **160b** in an equilibrium ratio of 3:1.

Table 5

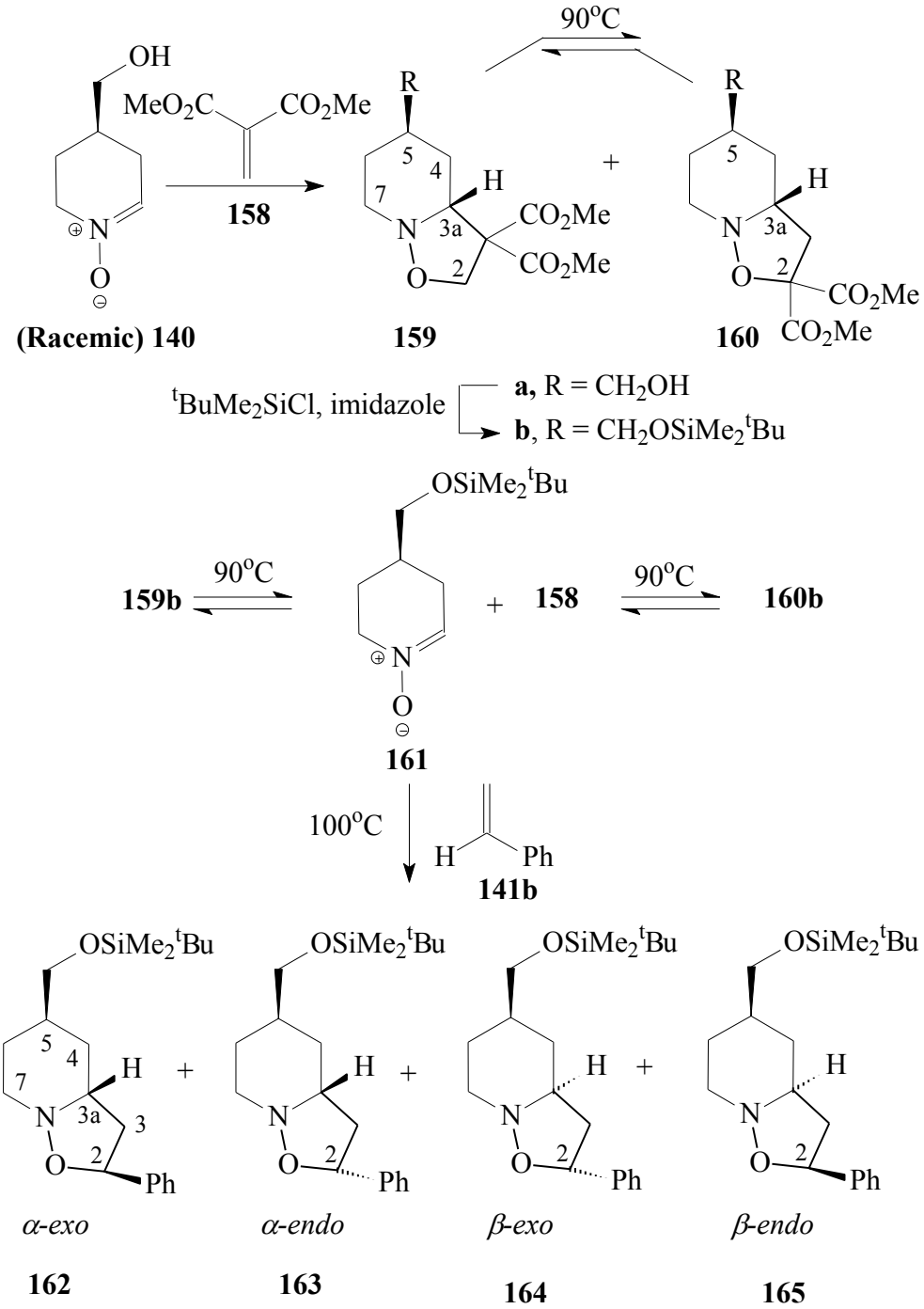
^{13}C NMR Chemical Shifts of compounds Studied in $CDCl_3$ at +25°C

Compound	% Invertomer[c]		C-2	C-3	C-3a	C-4	C-5	C-6	C-7
via α-mode									
142a	*cis*-**A**	88	77.3	35.4	59.4	28.1	32.5	27.6	49.1
	trans-**C**	12	76.1	40.1	61.2	30.1	34.0	25.6	50.7
142b	*cis*-**A**	90	78.9	38.8	59.9	28.3	32.6	27.6	49.4
	trans-**C**	10	77.7	43.2	61.7	30.1	34.0	25.7	51.1
143b	*cis*-**A**	84	81.7	38.3	60.7	28.4	33.0	27.7	51.9
	trans-**C**	16	78.9	44.2	62.5	29.8	33.9	25.7	51.3
149	*trans*-**C**	65	75.2	57.1	62.9	27.1	33.6	25.2	51.3
	cis-**A**	35	75.7	56.7	62.4	26.5	32.7	26.0	48.6
150	*cis*-**A**	Solo	80.2	54.4	64.0	27.4	32.9	27.2	52.3
145	*cis*-**A**	80	84.3	39.6	59.9	27.9	32.6	27.5	50.2
	trans-**C**	20	80.0	44.9	61.6	29.5	33.7	25.3	51.2
159b	*trans*-**C**	Solo	71.8	67.0	71.6	29.3	38.3	27.3	54.5
160b	*cis*-**A**	84	87.0	38.1	60.3	27.7	32.7	27.6	50.9
	trans-**C**	16	83.3	42.7	61.7	29.7	33.3	25.3	51.4
162	*cis*-**A**	84	78.8	38.9	60.0	28.3	32.7	27.7	49.5
	trans-**C**	16	77.7	43.3	61.9	30.2	33.8	25.6	51.2
168a	*cis*-**A**	83	77.3	35.3	59.1	28.3	29.5	27.6	48.8
	trans-**C**	17	76.1	40.0	61.0	30.4	30.5	25.8	50.7
168b	*cis*-**A**	88	78.8	38.8	59.7	28.3	29.6	27.6	49.1
	trans-**C**	12	77.7	43.1	61.6	30.5	30.5	25.9	50.9
via β-mode									
144a	*trans*- **F**	Solo	76.6	39.8	65.7	32.1	38.7	27.9	53.9
144b	*trans*- **F**	Solo	78.2	42.8	66.2	32.1	38.6	27.9	54.0
156	*trans*- **F**	Solo	80.5	44.6	66.1	31.6	38.4	27.5	54.1

[c]Refers to invertomer **A**, **C** or **F** in Scheme 44.

When the thermolysis was carried out in the presence of styrene, the intervening nitrone **161** was trapped by undergoing stereoselctive cycloaddition to give a mixture of adducts **162-165** in a ratio of 94:3:3:0. The exercise has thus demonstrated a suitable way to protect a nitrone functionality and also paved the way to examine the effect of changing the substituent C(4)-CH_2OH in 8 to C(4)-$CH_2OSitBuMe_2$ in **161** on the stereoselection and composition of nitrogen invertomers of the cycloadducts (*vide infra*).

The presence of −N−O− moiety in an organic molecule has a distinctive place in conformational analysis [84]; oxygen being next to nitrogen raises the barrier to nitrogen inversion to such an extent that the individual invertomers can be identified by NMR spectroscopy [83]. Orientation of the nitrogen lone pair with respect to the bridgehead hydrogen and the *trans*-/*cis*-fused invertomer ratio dictate the regiochemical outcome of the peracid oxidation process leading to the second-generation nitrones (*vide supra*) (Scheme 42). Therefore, the proper utilization of these second-generation nitrones requires prior information on the stereochemistry of the ring fusion. we have examined the conformational aspects as well as composition of the nitrogen invertomers by NMR spectroscopy. The ^{13}C chemical shifts in $CDCl_3$ were assigned on the basis of DEPT experiment results, general chemical shifts arguments and consideration of substituent effects, and are given in (Table 4).



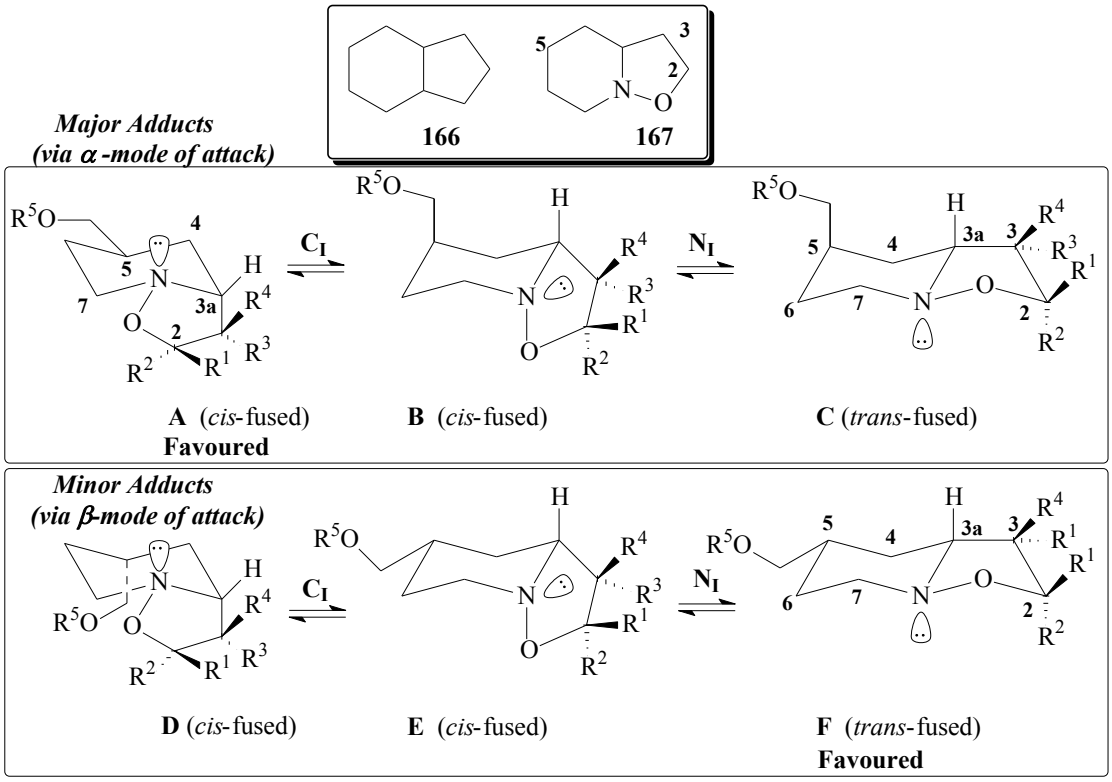
Ratio	% Yield
162 / 163 / 164 / 165	**162 + 163 + 164 + 165**
94 : 3 : 3 : ~0	83%

Scheme 45.

At ambient temperature, the ^{1}H and ^{13}C NMR spectra of these compounds show well separated signals for the two invertomers in $CDCl_3$. Integration of the relevant peaks gives the population trends in these systems (Table 4, 3rd column).

For the 6/5 fused carbocyclic compound **166**, the ΔG^{o} value of 2.09 kJ/mol at 25°C favours the *trans*- over the cis-fused isomer (Scheme 46) [93]. Both **167** (the heterocyclic counterpart of **166**), and its derivatives having substituents at the 2-, 3- and an ester group at the 5- position are also reported to favour, in most cases, the trans invertomers [83,93] The currently prepared major isoxazolidines, obtained by α-mode of attack, can, in principle, exist in three different chair conformations: the *cis*-fused pair A and B and the trans isomer C (Scheme 46). While the cis pair is in rapid equilibrium by chair inversion (CI), one of the cis conformers B is converted into the trans invertomer C by a relatively slow nitrogen inversion process (NI). The NMR spectra, both ^{1}H and ^{13}C, for some of the compounds show peaks due to two distinct isomers, a major and a minor invertomer. With respect to the six-membered ring, both cis-fused A and trans-fused C has one axial substituent at C(3a) and C(5), respectively, while *cis*-fused B has two energetically destabilizing axial substituents at C(5) and N. As such the major cycloadducts, obtained by an α-mode of attack, are expected to remain as A and/or C. For the reasons discussed above, the minor isoxazolidines, obtained by β-mode of attack, should have an overwhelming preference for the trans-fused invertomer F since it is free of any destabilizing axial group. The conformer D having two axial substituents is anticipated to be the least favoured. Note that our objective is to have the ixoxazolidines exist as the cis-fused invertomer in order to get the desired second-generation aldonitrones *via* peracid oxidation (*vide supra*). While this may not be achieved in the case of the *trans*-fused

invertomer F, the overwhelmingly predominant cycloaddition products (*via* an α-mode of attack), is, however, expected to be in the desired *cis*-form A.



Scheme 46.

Isoxazolidine **146** (Scheme 43) has been shown to exist in a *cis*-A/*trans*-C ratio of 55:45 (Scheme 46) [94]. A comparison between compound **146** and **142b** (Scheme 43), both having a phenyl group at C(2), may be helpful in identifying the stereochemistry of the ring fusion in the latter. Since the axially disposed CH_2OH substituent at C(5) of **142b**, being larger in size than the ester substituent in **146**, is expected to destabilize its trans **142**-C as well as *cis* **142**-B conformers; the relative proportion of *cis*-**10b**-A is anticipated to increase in compare to that of compound **146** (Scheme 46). As evident from Table 4, this is indeed the case; the *cis*-A isomer becomes the overwhelmingly major invertomer

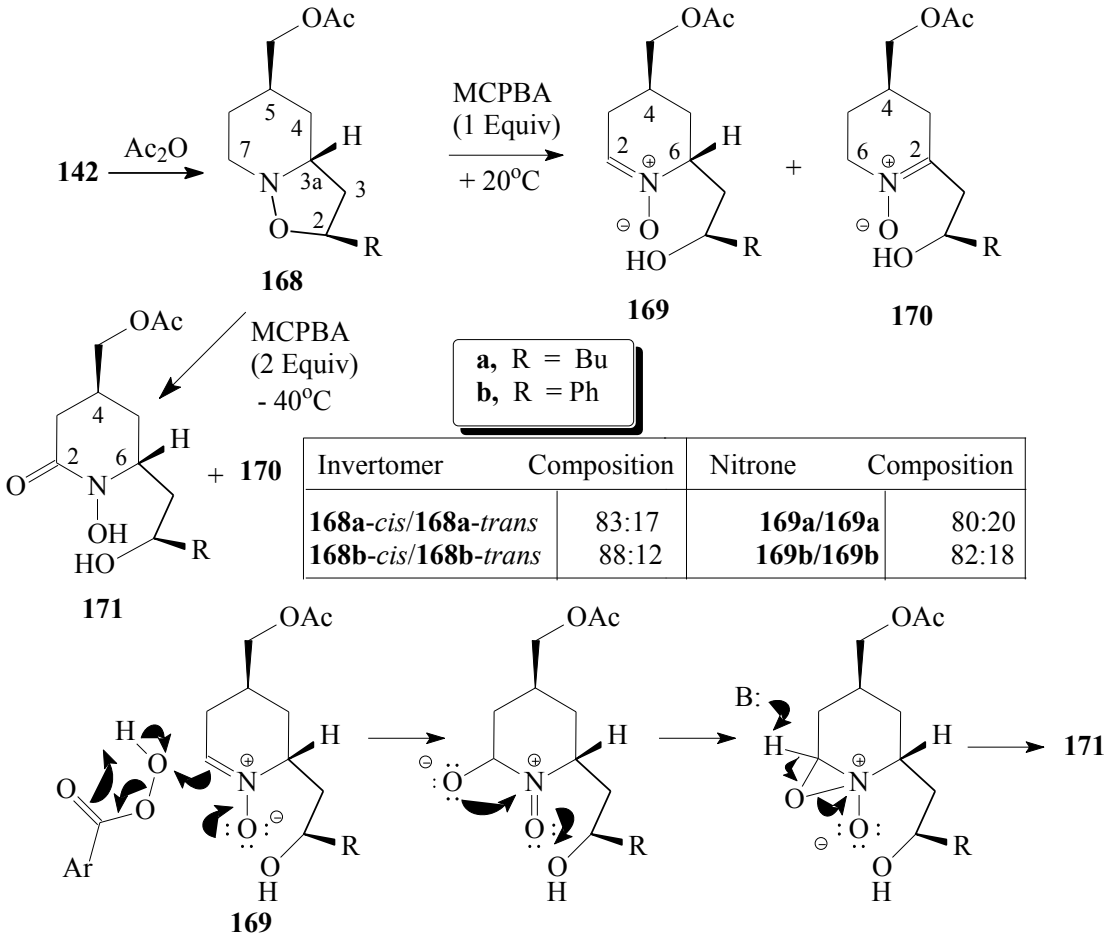
for all the cycloadducts obtained via α-mode of attack, except **159b** (Scheme 45) which would be destabilized in *cis*-A as a result of placement of an axially-oriented tertiary sustituent (akin to a t-butyl group) at C3a. The correctness of the assignment of the configuration is based on the rationale detailed in the subsequent discussion.

The C(2)H of the cis invertomers of 6/5-fused isoxazolidines is known to appear at higher frequency compared to its trans invertomers [94,95]. This is indeed found to be the case for the current compounds in $CDCl_3$; the C(2)H of the cis-A invertomers invariably appeared at higher frequency compared to their *trans*-C isomers (Scheme 46). The axially disposed C(3a)H of *trans*-C, as expected, appeared at lower frequency in comparison to the corresponding equatorially disposed proton of *cis*-A (See Experimental). The axial substituent at C(3a) of the *cis* conformer A will have γ–gauche interactions with C(5) and C(7) and as such these carbon signals are expected to be shielded in comparison to the *trans*-C as is evident from Table 4. In *cis*-A all the carbons appeared at lower frequency except C-2 and C-6.

Where only one invertomer is observed as in the cases of **144a**, **144b**, **156**, **159b** (the minor products obtained *via* β-mode of attack), the C(2), C(3), C(3a) and C(7) chemical shifts match those of the *trans*-C invertomers, and we can therefore conclude that these compounds exist almost exclusively in the *trans*-F conformation (Scheme 44) (Table 4). The presence of 1,3-diaxial interaction exclude the participation of conformer *cis*-D in the equilibration process (Scheme 46). In the absence of D & E equilibration, the stabilization arising out of entropy gain will be lost; as such the all equatorial *trans*-invertomer F is expected to be overwhelmingly favoured over *cis*-E.

To get an idea about the magnitude of nitrogen inversion barriers in these compounds, **142b** was selected as a representative example. The nitrogen inversion barrier, $\Delta G^{\#}$, was determined to be 71.3 kJ/mol for a major to minor inversion at 35°C in toluene-d_8. Simulations of exchange-affected proton spectra, corresponding to two non- coupled sites exchange with unequal populations, were carried out as described elsewhere [95]. For **142b** in toluene-d_8, the C(2)H signals at δ5.42 (major, dd, J 1.7, 4.9 Hz) and 5.28 ppm (minor) in a 83:17 ratio at +30°C were utilized. For such a high free energy of activation barrier, the extremely fast peracid oxidation process (presumably with a lower activation barrier) is not expected to follow the Curtin-Hammett principle [81]; as such the trans and cis invertomers in a ratio of x:y should afford the keto- and aldo-nitrones, respectively, in a similar ratio. In order to ascertain the correctness of the assignment of the configuration of the invertomers, we carried out the peracid induced ring opening of isoxazolidines **168a** and **168b** (Scheme 47). The isoxazolidine **168a**, having the cis and trans invertomers in a 83:17 ratio, on treatment with m-chloroperbenzoic acid (MCPBA) gave a mixture of the aldo- (**169a**) and keto-nitrone (**170a**) in a 80:20 ratio. For the corresponding ring opening reaction of the isoxazolidine **168b**, having the *cis* and *trans* invertomers in a 88:12 ratio, a mixture of the aldo- (**169b**) and keto-nitrone (**170b**) in a ratio of 82:18 was obtained. It is indeed gratifying to see the ratio in favour of the synthetically more useful second-generation aldonitrones. One interesting finding was that the treatment of the isoxazolidines **168** with two equivalents of MCPBA at -40°C afforded the N-hydroxyamides **171**, presumably via further oxidation of the aldonitrones with peracid as shown in (Scheme 47). The formation of amide thus paves the way to obtain acyclic

compounds from the cyclic piperidine system *via* hydrolysis of the amide functionality in **171**.

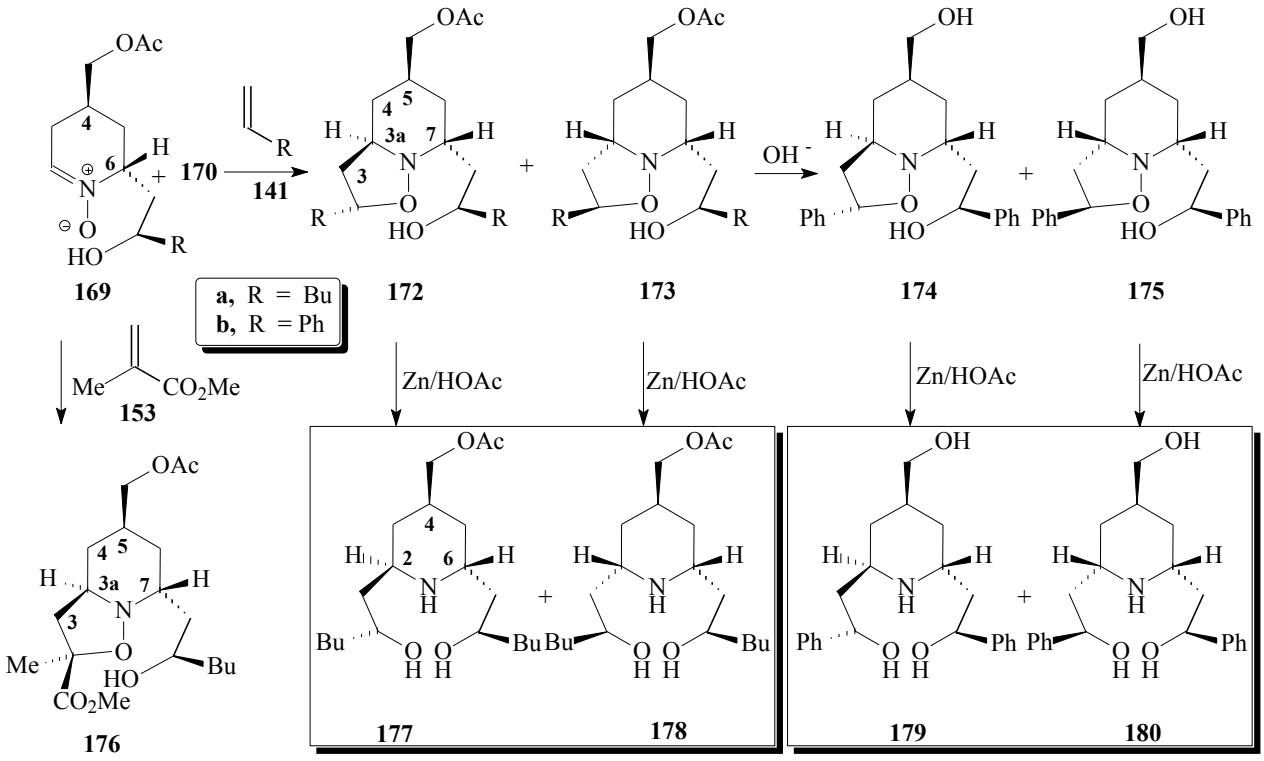


Invertomer	Composition	Nitrone	Composition
168a-*cis*/**168a**-*trans*	83:17	**169a/169a**	80:20
168b-*cis*/**168b**-*trans*	88:12	**169b/169b**	82:18

Scheme 47.

Next, we explored the cycloaddition reaction of the second-generation nitrones **169** and **170** with the alkenes **141**. Under the reaction conditions, the ketonitrones remained inactive while the aldonitrones **169** afforded the cycloadducts **172** and **173** (Scheme 48). While the aldonitrone **169a** afforded **172a** and **173a** in a 2:1 ratio, the corresponding ratio for **172b** and **173b** was found to be 1:1.5. For the addition of 1-hexene (**141a**) the face

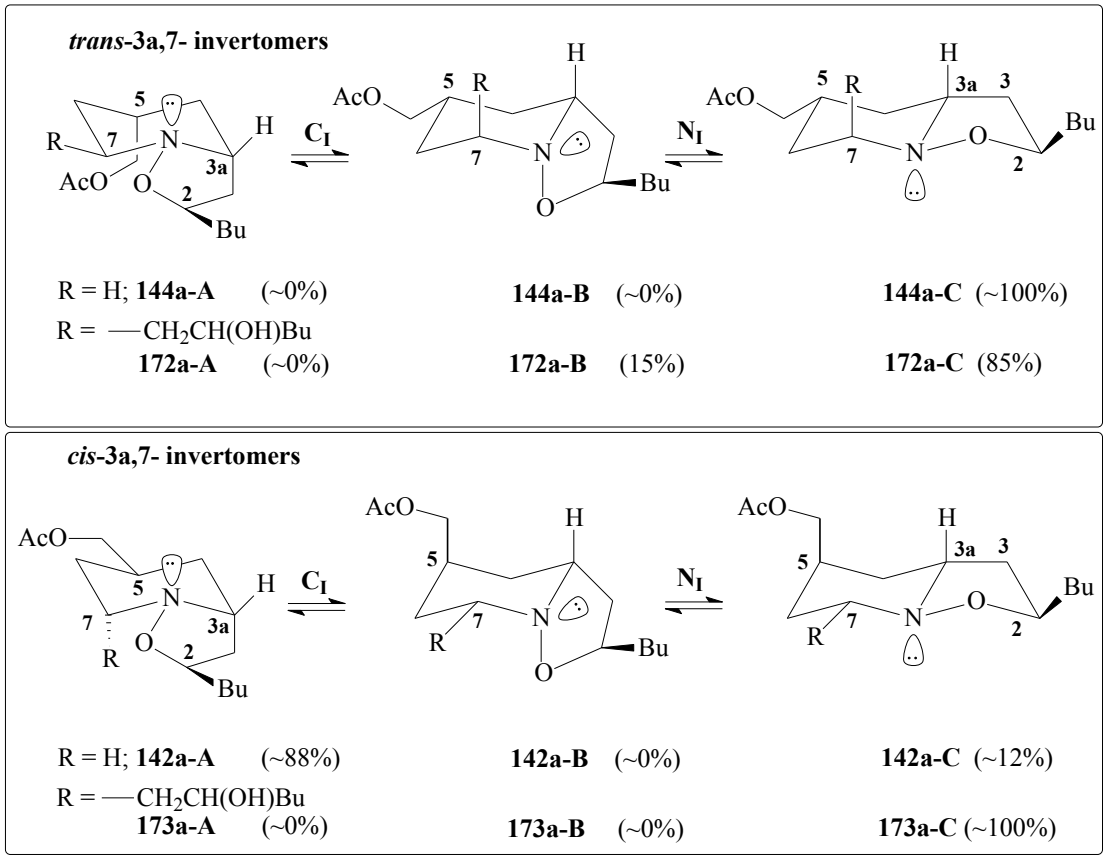
selectivity is thus dictated by the steric influence of the substituent at C(6) so as to force the alkene to approach from the β-face of the nitrone, while styrene (**141b**) prefers to approach the nitrone from it's α-face. The face selectivity is modest in these additions; however, we are unable to rationalize the difference in the face selectivity observed in the addition reactions of these two alkenes. The stereochemistry of these addition reactions were confirmed by chemical conversion into the ring opened products by cleaving the N-O bond of the cycloadducts with zinc/acetic acid. The NMR spectra of the amine **178** ($C_{20}H_{39}NO_4$), obtained from adduct **173a**, confirmed its symmetric nature; as expected the ^{13}C NMR spectrum revealed the presence of 12 carbon signals, whereas the isomeric 2,6-trans substituted amine **177**, obtained from adduct **172a**, displayed 18 different carbon signals as a result of its unsymmetrical nature. (In the unsymmetrical amine the signals at δ14.1 and 22.8 ppm belonged to two carbons in each case). The nonseparable mixture of adducts **172b** and **173b** upon hydrolysis was converted into a separable mixture of compounds **174** and **175**. The N-O bond cleavage of **175** afforded the symmetrical cis amine **180**, while **174** led to the unsymmetricl *trans* amine **179**.



Scheme 48.

Finally, we explored the face selectivity in the cycloaddition of the aldonitrone **169a** with 1,1-disubstituted alkene, methyl methacrylate (**153**). To our surprise, the addition was found to be highly face selective; adduct **176** and a nonseparable mixture of three minor adducts were obtained in a ratio of 88:12. The stereochemistry of the adduct was based on the approach of the alkene from the β-face of the nitrone to give 2,6-*trans* substituted adduct **176**. The assignment of stereochemistry was based on the observed stereochemistry of the addition reaction of the second-generation nitrones **169** to 1-hexene and styrene. In both cases the 3a,7-*trans* substituted adducts **172a** and **174** were found to have two invertomers, whereas the 3a,7-*cis* substituted adducts **173a** and **175** gave sharp NMR signals and revealed the presence of a single invertomer in each case. The major

adduct **176** in the nitrone **169a**-methylmethacrylate addition reaction was also found to have a single invertomer and as such was assigned the 3a,7-*trans* configuration. The conformational analysis revealed that while the adduct **142a** remained as a mixture of two invertomers A and C in a ratio of 88:12 (*vide supra*), the presence of two axial groups in A and B forces the 3a,7-*cis*-substituted adduct **173a** to remain exclusively in the invertomeric form of **173a**-C (Scheme 49). While the adduct **144a** remained exclusively in the invertomeric form of **144a**-C (*vide supra*), the 3a,7-*cis*-substituted adduct **172a** remained in the invertomeric forms of **172a**-B and **172a**-C in a ratio of 28:72 (See experimental). The presence of **172a**-B in sizable proportion is justified even though it has two axial groups; the additional gauche interaction between C(7)R and N-O in **172a**-C is absent in the conformer **172a**-B, thereby encouraging its presence.



Scheme 49.

A systematic study of the stereochemistry associated with the cycloaddition of a C(4)-substituted and second-generation C(4),(6)-disubstituted six-membered cyclic nitrones has been carried out for the first time. The remarkable *exo/endo*- and face-selectivity observed in our study reflects the scope inherent in these important cycloaddition reactions. The study suggests that a bulkier tertiary substituent at C(4) may freeze the invertomer exclusively in the cis-fused form and thus would lead to the exclusive formation of the synthetically important second-generation aldonitrones *via* peracid induced ring opening of the cycloadducts.

4.3 Experimental

4.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTI.R spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). Piperidine 4-carboxylic acid, 1-hexene, styrene, methyl methacrylate, methyl crotonate, m-chloroperbenzoic acid, from Fluka Chemie AG (Buchs, Switzerland) were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N_2. 4-Piperidinemethanol **(138)** was prepared from methyl ester of piperidine 4-carboxylic acid as described [73]. Dimethyl methylenemmalonate was prepared using the literature procedure [92].

4.3.2. *N*-hydroxy-4-Piperidinemethanol (139)

To a stirring solution of amine **138** (15 g, 130 mmol) with methanol (200 mL) in presence of selenium dioxide (0.7 g) at 0°C under N_2 was added dropwise a 30% H_2O_2 solution (18.5 g, 163 mmol) in 15 min. The mixture was then stirred at 20°C for 8 h. Sodium borohydride (2 g, 54 mmol) was added to the above mixture and stirring continued for 2 h. After removal of the solvent, the residual mixture was taken up in saturated K_2CO_3 solution (40 mL) and extracted with CH_2Cl_2/MeOH (9:1) (4×50 mL). The combined organic layers was dried (Na_2SO_4), concentrated and the residual liquid was purified by

chromatography over silica using 1:1 ether/methanol mixture as eluant to give the hydroxylamine **139** as a white solid (10.2 g, 60%). *m/z* 131 [M^+]; mp 103-104ºC (methanol-ether), (Found: C, 54.8; H, 9.9; N, 10.6. $C_6H_{13}NO_2$ requires C, 54.94; H, 9.99; N, 10.68 %.); ν_{max} (KBr) 3226, 2963, 2911, 2856, 2830, 1656, 1480, 1446, 1383, 1276, 1242, 1133, 1103, 1037 and 996 cm^{-1}; δ_H (500 MHz, 9:1 $CDCl_3/CD_3OD$, +25°C) 3.42-3.28 (4H, m, C2-$H_a\underline{H}_e$, C6-$H_a\underline{H}_e$ and $C\underline{H}_2O$), 2.50-2.44 (2H, m, C2-$\underline{H}_aH_e$, C6-$\underline{H}_aH_e$), 1.81-1.31 (5H, m, C3-$\underline{H}_2$, C4-$\underline{H}$, C5-$\underline{H}_2$); δ_C (500 MHz, 9:1 $CDCl_3/CD_3OD$, +25°C) 66.6 (2C), 58.1, 37.2, 28.2 (2C). The hydroxylamine was partially soluble in $CDCl_3$, but soluble in a $CDCl_3/CD_3OD$ mixture.

4.3.3. 4-Hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide (140)

To a solution of the hydroxylamine (5.24 g, 40 mmol) in EtOH or MeOH (50 mL) was added yellow HgO (18.0 g, 84 mmol) and the mixture was stirred using a magnetic stir bar at 35°C for 2 h or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and $MgSO_4$. The bed was washed with liberal excess of ethanol. The formation of the nitrone was assumed quantitative for the percent yield calculation in the subsequent cycloaddition reactions. δ_H (500 MHz, CD_3OD +25°C) 7.34-7.33 (1H, m), 3.87-3.72 (2H, m, C6-$\underline{H}_2$), 3.57-3.45 (2H, m, $C\underline{H}_2O$), 2.66-2.56 (1H, m, C3-$H_a\underline{H}_e$), 2.30-2.20 (1H, m, C3-$\underline{H}_aH_e$), 2.11-2.03 (1H, m, C5-$H_a\underline{H}_e$), 1.97-1.87 (1H, m, C4-$\underline{H}$), 1.83-1.71 (1H, m, C5-$\underline{H}_aH_e$); δ_C (500 MHz, CD_3OD, +25°C) 143.6, 65.6, 57.7, 32.3, 29.5, 26.2. The nitrone can not be purified further since upon concentration it undergoes dimerization and other side reactions.

4.3.4. Reaction of nitrone 140 with 1-hexene (141a)

A solution of nitrone (10 mmol) in EtOH (40 mL) containing 1-hexene **(141a)** (6 mL) was heated at 90°C for 24 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give **142a** containing minor amount of **144a**. Continued elution gave a pure sample of the major adduct **142a** as a colourless liquid. The minor diastereomer **144a** was obtained in the pure form after repeated chromatography of the fraction containing the mixture of **142a** and **144a**. The combined yield of the cycloadducts was found to be (1.67 g, 78%).

The C(2) of the major adduct **142a** appeared at δ4.38 (major invertomer) and 4.02 ppm (minor invertomer). The overlapping C(2)H signal for the isomer **144a** appeared at δ4.06 ppm. The complete ^{1}H NMR analysis of the C(2)H of crude and the separated fraction revealed the ratio of the isomers **142a-145a** as 93:~0:7:~0, respectively.

4.3.4.1 Major Diastereomer 142a

(Found: C, 67.4; H, 10.7; N, 6.5. $C_{12}H_{23}NO_2$ requires C, 67.57; H, 10.87; N, 6.57 %.); ν_{max} (neat) 3352, 2954, 2925, 2858, 1455, 1379, 1260, 1100, 1037, 963, and 765 cm^{-1}. The major and minor invertomer at 25 °C was found to be in a ratio of 88:12 as determined by integration of the C(2)H at δ4.38 (major) and 4.02 (minor) ppm.

4.3.4.1.1. Major invertomer of 142a

δ_H (500 MHz, $CDCl_3$, 25 °C) 4.42-4.34 (1H, m, C2-H), 3.66-3.58 (1H, m, C3a-H), 3.49-3.41 (2H, m, CH_2OH), 3.08 (1H, td, *J* 3.2, 10.4 Hz, C7-H_aH_e), 2.92 (1H, br, OH), 2.68 (1H, ddd, *J* 2.5, 10.3, 12.8 Hz, C7-H_aH_e), 2.35 (1H, dt, *J* 9.5, 11.9 Hz, C3-H_aH_b), 2.00 -1.20 (12H, m, $(CH_2)_3$, C3-H_aH_b, C4-H_2, C5-H, C6-H_2), 0.90 (3H, t, *J* 6.8 Hz, Me); δ_C

(500 MHz, $CDCl_3$, 25 °C) 77.3, 67.1, 59.4, 49.1, 35.4, 35.2, 32.5, 28.4, 28.1, 27.6, 22.7, 14.0.

4.3.4.1.2. Minor invertomer 142a

Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, 25 °C) 4.07-3.97 (1H, m, C2-H), 3.64-3.60 (2H, m, CH_2OH), 3.33-3.27 (1H, m, C3a-H), 2.61-2.51 (1H, m, C7-H_aH_e), 2.04-1.94 (1H, m, C3-H_aH_b); δ_C (500 MHz, $CDCl_3$, 25 °C) 76.1, 63.2, 61.2, 50.7, 40.1, 35.0, 34.0, 30.1, 28.0, 25.6, 22.7, 14.0.

4.3.4.2. Minor diastereomer 144a

The sharp proton and carbon signals at +25 °C or -30 °C indicated the presence of a single invertomer. Coluorless liquid (Found: C, 67.7; H, 10.9; N, 6.5. $C_{12}H_{23}NO_2$ requires C, 67.57; H, 10.87; N, 6.57%.); ν_{max} (neat) 3386, 2928, 2859, 1460, 1379, 1259, 1099, 1049, 1017, 898, and 779 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.10-4.02 (1H, m, C2-H), 3.56-3.46 (2H, m, CH_2O), 3.51-3.43 (1H, m, C3a-H), 2.56-2.46 (1H, m, C7-H_aH_e), 2.30-2.20 (1H, m, C7-H_aH_e), 2.02-1.20 (13H, m, $(CH_2)_3$, C3-H_2, C4-H_2, C5-H, C6-H_aH_e, OH), 1.14 (1H, q, *J* 12.2 Hz, C6-H_aH_e), 0.90 (3H, t, *J* 6.8 Hz, Me); δ_C (500 MHz, $CDCl_3$, +25 °C) 76.6, 67.2, 65.7, 53.9, 39.8, 38.7, 35.0, 32.1, 28.0, 27.9, 22.7, 14.0.

4.3.5. Reaction of nitrone 140 with styrene (141b)

A solution of nitrone **140** (10 mmol) in EtOH (40 mL) containing styrene (4 mL) was heated at 90 °C for 4 h under N_2 in a closed vessel. After removal of the solvent and excess alkene, the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give **142b** containing minor amount of **144b**. Continued elution gave a pure sample of the major adduct **142b** as

white crystals. Finally, a fraction containing **142b** and **143b** was obtained; repeated chromatography enriched the fraction to a ratio of 4:96 for the isomers **142b/ 143b**. The combined yield of the cycloadducts was found to be (1.98 g, 85%). The fraction containing the mixture of **142b** and **144b** was crystallized to separate the major adduct **142b**, while the mother liquor upon repeated chromatography gave the minor adduct **144b**.

A careful ^{1}H NMR ($CDCl_3$, -40° C) analysis of the crude reaction mixture and the separated fractions revealed the presence of the isomers **142b-144b** in a ratio of 93:5:2:~0, respectively. The C(2) of the major adduct **142b** appeared at δ5.39 (major invertomer) and 5.02 ppm (minor invertomer). The corresponding proton for the isomer **143b** appeared at δ5.23(1H, apparent t, *J* 8.5 Hz). The C(2)H signal for the isomer **144b** appeared as a dd (*J* 4.0, 9.8 Hz) at δ5.05 ppm.

4.3.5.1. Major Diastereomer 142b

Mp 104–105 °C (ether-dichloromethane); *m/z* 233.1 [M^+]; (Found: C, 72.0; H, 8.1; N, 5.9. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00 %.); ν_{max} (KBr) 3406, 2925, 2844, 1450, 1380, 1308, 1253, 1090, 1052, 955, 768, 701, and 630 cm^{-1}. The major and minor invertomer at 25 °C was found to be in a ratio of 90:10 as determined by integration of the C(2)H. (The ratio becomes 93:7 at -40 °C).

4.3.5.1.1. Major invertomer of 142b

δ_H (500 MHz, $CDCl_3$, +25 °C) 7.44-7.24 (5H, m, Ph), 5.39 (1H, dd, *J* 3.7 and 9.8 Hz, C2-H), 3.88-3.80 (1H, m, C3a-H), 3.54-3.42 (2H, m, CH_2OH), 3.26-3.18 (1H, td, *J* 3.3, 10.4 Hz, C7-H_aH_e), 2.82 (1H, ddd, *J* 2.2, 10.6, 12.8 Hz, C7-H_aH_e), 2.70 (1H, q, *J* 11.2 Hz, C3-H_aH_b), 2.50 (1H, br, OH), 2.05 -1.60 (5H, m, C3-H_aH_b, C4-H_2, C5-H, C6-

$H_a\underline{H}_e$), 1.38-1.24 (1H, m, C6-$\underline{H}_aH_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 142.3, 128.4 (2C), 127.6, 126.4 (2C), 78.9, 67.1, 59.9, 49.4, 38.8, 32.6, 28.3, 27.6.

4.3.5.1.2. Minor invertomer of 142b.

Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, +25°C) δ 5.06-4.98 (1H, m, C2-$\underline{H}$; at -40 °C the signal becomes a dd (*J* 4.2, 9.6 Hz)), 3.70-3.62 (2H, m, C$\underline{H}_2$OH), 3.39-3.31 (1H, m, C3a-$\underline{H}$), 2.38-2.26 (1H, m C3-$\underline{H}_aH_b$); δ_C (500 MHz, $CDCl_3$, +25 °C) 141.6, 128.3 (2C), 127.7, 126.7 (2C), 77.7, 63.2, 61.7, 51.1, 43.2, 34.0, 30.1, 25.7.

4.3.5.2. Minor diastereomer 143b

We were unable to obtain the distereomer **143b** in pure form even after repeated chromatography. Finally, a fraction containing adduct **143b** along with minor amount (~4%) of the isomer **142b** was analyzed. The proton and carbon signals at 25 °C or -40 °C indicated the presence of two invertomers for **143b** in a 84:16 ratio as indicated by the C(2)H ($CDCl_3$, -40°C) at δ 5.28 (1H, t, *J* 8.5 Hz) and 5.10 (1H, t, *J* 8.4 Hz). The invertomer ratio becomes 80:20 at + 25 °C. Colorless liquid; (Found: C, 71.9; H, 8.3; N, 6.1. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.); ν_{max} (neat) 3336, 2921, 2859, 1448, 1355, 1279, 1258, 1094, 1034, 961, 756, 700, and 673 cm^{-1}.

4.3.5.2.1. Major Invertomer of 143b

δ_H (500 MHz, $CDCl_3$, 25 °C) 7.52-7.20 (5H, m, Ph), 5.24 (1H, t, *J* 8.5 Hz, C2-$\underline{H}$), 3.90-3.78 (1H, m, C3a-$\underline{H}$), 3.53-3.41 (2H, m, C$\underline{H}_2$OH), 3.27 (1H, td, *J*3.7, 11.0 Hz, C7-$H_a\underline{H}_e$), 2.73 (1H, t, *J* 12.2 Hz, C7-$\underline{H}_aH_e$), 2.59-2.47 (1H, m, C3-$\underline{H}_aH_b$), 2.38 (1H, q, *J* 12.2

Hz, C3-$H_a\underline{H}_b$), 2.09 (1H, apparent d, *J* 14.6 Hz, C6-$H_a\underline{H}_e$), 1.85-1.57 (4H, m, C4-$\underline{H}_2$, C5-$\underline{H}$, O$\underline{H}$), 1.31 (1H, apparent q, *J* 12.2 Hz, C6-$\underline{H}_aH_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 143.2, 128.3 (2C), 127.1, 125.6 (2C), 81.7, 67.3, 60.7, 52.0, 38.3, 33.0, 28.4, 27.7.

4.3.5.2.2. Minor Invertomer of 143b

δ_C (500 MHz, CDCl3, +25 °C) 143.2, 128.3 (2C), 127.1, 125.6 (2C), 78.9, 63.6, 62.5, 51.3, 44.2, 33.9, 29.8, 25.7.

4.3.5.3. Minor diastereomer 144b

Colourless liquid**;** (Found: C, 71.8; H, 8.0; N, 5.8. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00 %.). The signals were sharp; the ^{1}H spectrum revealed the presence of a single invertomer. ν_{max}(neat) 3356, 2921, 2849, 1449, 1364, 1324, 1260, 1099, 1051, 1011, 948, 912, 760, 730 and 699 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 7.47-7.23 (5H, m, Ph), 5.05 (1H, dd, *J* 4.9, 9.8 Hz, C2-$\underline{H}$), 3.54 (3H, m, C3a-$\underline{H}$, C$\underline{H}_2$OH), 2.68 (1H, apparent t, *J* 9.8 Hz, C7-$H_a\underline{H}_e$), 2.60-2.50 (1H, m C7-$\underline{H}_aH_e$), 2.37 (1H, q, *J* 11.0 Hz, C3-$\underline{H}_aH_b$), 2.23-2.15 (1H, m, C3-$H_a\underline{H}_b$), 2.08 (1H, d, *J* 12.2 Hz, C4-$H_a\underline{H}_e$), 2.01-1.89 (2H, m, C4-$\underline{H}_aH_e$, O$\underline{H}$), 1.76-1.64 (1H, m, C5-$\underline{H}$), 1.48 (1H, dq, *J* 3.7, 13.4 Hz, C6-$H_a\underline{H}_e$), 1.21 (1H, q, *J* 12.2 Hz, C6-$\underline{H}_aH_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 141.6, 128.4 (2C), 127.8, 126.7 (2C), 78.2, 66.9, 66.2, 54.0, 42.8, 38.6, 32.1, 27.9.

4.3.6. Lithium aluminium hydride reduction of ester cycloadduct 146 to 142b

To a stirred solution of ester adduct **146** of known configuration[9] (100 mg, 0.33 mmol) in ether (15 mL) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1

g) and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using a 95:5 CH_2Cl_2/methanol as the eluant to give **142b** as a white solid (71 mg, 92%), which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.5.

4.3.7. Lithium aluminium hydride reduction of ester cycloadduct 147a to 144a

A sample of adduct **147a** was reduced with $LiAlH_4$ using procedure as described in Section 3.6 to give **144a** as a coluorless liquid (93% yield)**,** which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.2.

4.3.8. Lithium aluminium hydride reduction of ester cycloadduct 147b to 144b

A sample of adduct **147b** was reduced with $LiAlH_4$ using procedure as described in Section 4.3.6 to give **144b** as a colourless liquid (90% yield)**,** which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.5.3.

4.3.9. Reaction of nitrone 140 with methyl crotonate (148)

A solution of nitrone **140** (5.0 mmol) in EtOH (20 mL) containing methyl crotonate (**148**) (4 mL) was heated at 90 °C for 10 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was purified by chromatography over silica using 95:5 ether/methanol as eluant to give a non-separable mixture of adducts **149-151** as a colourless liquid (0.974 g, 85%). We were unable to separate the isomers even after repeated chromatography. (Found: C, 57.5; H, 8.2; N, 6.0.

$C_{11}H_{19}NO_4$ requires C, 57.63; H, 8.35; N, 6.11 %.); ν_{max} (neat) 3380, 2929, 2855, 1730, 1439, 1392, 1379, 12.97, 1265, 1203, 1179, 1113, 1090, and 1029 cm^{-1}.

A careful ^1H NMR ($CDCl_3$, -40° C) analysis of the crude reaction mixture and the separated fractions revealed the presence of the isomers **149-151** in a respective ratio of 81:16:3. The C(2) of the major adduct **149** appeared at δ4.50 (quint, *J* 5.8 Hz, major invertomer) and 5.01 ppm (quint, *J* 6.1 Hz, minor invertomer) in a 65:35 ratio. The ratio becomes 60:40 at +25° C. The corresponding proton of the isomers **150** and **151** appeared at δ4.41 (qd, *J* 6.5, 8.9 Hz, single invertomer), and 4.29 (quint, *J* 6.1 Hz, single invertomer). The CO_2Me singlets of the **149** appeared at δ3.75 (major invertomer), and 3.79 (minor invertomer) and that of **150** appeared at 3.77 ppm. The C(2)Me ($CDCl_3$, +25° C) signal for the isomer **149, 150** and **151** appeared at δ1.33 (d, *J* 6.4 Hz), 1.50 (d, *J* 6.4 Hz), and 1.44 (d, *J* 6.4 Hz), respectively.

4.3.9.1. Major invertomer of major diastereomer 149

δ_C (500 MHz, $CDCl_3$, +25 °C) 172.1, 75.2, 64.5, 62.9, 57.1, 52.3, 51.3, 33.6, 27.1, 25.2, 19.3.

4.3.9.2. Minor invertomer of major diastereomer 149

δ_C (500 MHz, $CDCl_3$, +25 °C) 173.6, 75.7, 66.6 (CH_2O), 62.4, 56.7, 51.8 (OMe). 48.6, 32.7, 26.5, 26.0, 19.5.

4.3.9.3. Minor diastereomer 150

A single invertomer. δ_C (500 MHz, $CDCl_3$, +25 °C) 171.8, 80.2, 66.6 (CH_2O), 64.0, 54.4, 52.8, 52.3, 33.0, 27.4, 27.2, 22.7.

4.3.10. Reaction of nitrone 140 with methyl methacrylate (153)

A solution of nitrone **140** (5.0 mmol) in EtOH (20 mL) containing methylmethacrylate **(153)** (4 mL) was heated at 50°C for 6 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was separated by chromatography over silica using 95:5 ether/methanol as eluant to give **157** containing minor amount **154**. Continued elution afforded **22** along with minor amounts of **156** and **157**. The first fraction was rechoramatographed to obtain **157** as a colourless liquid. Adduct **154** was obtained from the second fraction as white crystals by crystallization. The mother liquor contained a mixture of **154-157**. The combined yield of the cycloadducts was found to be (1.05 g, 92%). The ^{13}C ($CDCl_3$, -40°C) spectrum of the crude mixture revealed the presence of C(2) of the major and minor invertomers of **154** at δ84.2 and 79.8 ppm in a 80:20 ratio. The corresponding signal for the isomer **157** appeared as a sole invertomer at 80.33, while the signals at δ84.8 and 80.6 in a respective ratio of 65:35 were assigned to C(2) of the major and minor invertomers of **156**. The ratio, as approximated, by analysis of ^{13}C and ^{1}H of the crude as well as the separated fraction revealed the presence of **154**, **156** and **157** in ratio of 92:5:3, respectively. We were unable to obtain a pure sample of the minor isomer **156** even after repeated chromatography.

4.3.10.1 Major Diastereomer 154

The major and minor invertomer at 25°C was found to be in a ratio of 80:20 as determined by integration of several non overlapping signals (the ratio remains the same at

-40 °C). Mp 72-73 °C (ether-dichloromethane); *m/z* 229 [M^+]; (Found: C, 57.5; H, 8.3; N, 6.1. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35; N, 6.11%); ν_{max} (KBr) 3337, 3234, 2953, 2926, 2862, 1746, 1727, 1454, 1442, 1370, 1300, 1255, 1127, 1183, 1086, 1026, 980, 962, 770, and 631 cm^{-1}.

4.3.10.1.1. Major invertomer of 154

δ_H (500 MHz, $CDCl_3$, +25 °C) 3.78 (3H, s, CO<u>Me</u>), 3.69-3.61 (1H, m, C3a-<u>H</u>), 3.53-3.42 (2H, m, C<u>H</u>$_2$OH), 3.16 (1H, d, *J* 7.5 Hz, C7-H$_a$<u>H</u>$_e$), 2.87 (1H, t, *J* 11.7 Hz, C7-<u>H</u>$_a$H$_e$), 2.68 (1H, t, *J* 10.0 Hz, C3-<u>H</u>$_a$H$_b$), 2.10 -1.50 (6H, m, C3-H$_a$<u>H</u>$_b$, C4-<u>H</u>$_2$, C5-<u>H</u>, C6-H$_a$<u>H</u>$_e$, O<u>H</u>), 1.49 (3H, s, <u>Me</u>), 1.35-1.19 (1H, m, C6-<u>H</u>$_a$H$_e$); δ_C ($CDCl_3$, +25 °C) 175.5, 84.3, 67.1, 59.9, 52.7, 50.2, 39.6, 32.6, 27.9, 27.5, 25.7.

4.3.10.1.2. Minor invertomer of 154

Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, +25°C): δ 3.39-3.30 (1H, m, C3a-<u>H</u>), 2.64-2.53 (1H, m, C7-H$_a$<u>H</u>$_e$), 2.50-2.35 (1H, m, C7-<u>H</u>$_a$H$_e$), 2.18-2.07 (1H, m, C3-H$_a$<u>H</u>$_b$); δ_C ($CDCl_3$, +25 °C) 175.5, 80.0, 63.3, 61.6, 52.7, 51.2, 44.9, 33.7, 29.5, 25.3, 24.8.

4.3.10.2 Minor Diastereomer 157

Colourless liquid**.** (Found: C, 57.4; H, 8.2; N, 5.9. $C_{11}H_{19}NO_4$ requires C, 57.62; H, 8.35; N, 6.11%.). The ^1H spectrum revealed the presence of a single invertomer. ν_{max} (neat) 3350, 2924, 2853, 1730, 1445, 1373, 1260, 1210, 1142, 1040, and 986 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 3.77 (3H, s, CO<u>Me</u>), 3.58-3.46 (3H, m, C3a-<u>H</u>, C<u>H</u>$_2$OH), 2.58-2.48 (1H, m, C7-H$_a$<u>H</u>$_e$), 2.47-2.35 (2H, m, C7-<u>H</u>$_a$H$_e$, O<u>H</u>), 2.20-2.12 (1H, m, C3-<u>H</u>$_a$H$_b$), 2.07-1.97 (1H, m, C3-H$_a$<u>H</u>$_b$), 1.92-1.82 (1H, m, C5-<u>H</u>), 1.73-1.60 (2H, m, C4-H$_a$<u>H</u>$_e$, C6-

$H_a\underline{H_e}$), 1.50 (3H, s, Me), 1.48-1.40 (1H, m, C4-$\underline{H_a}H_e$), 1.16 (1H, q, *J* 11.9 Hz, C6-$\underline{H_a}H_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 175.6, 80.5, 67.2, 66.1, 54.1, 52.6, 44.6, 38.4, 31.6, 27.5, 24.7.

4.3.11. Reaction of nitrone 140 with dimethyl methylenemalonate (158) and conversion of cycloadducts 159a and 160a to silylated ethers 159b and 160b

A solution of nitrone **140** (10 mmol) in methanol (40 mL) was reacted with dimethylmethylene malonate **(158)** (1.73 g, 12 mmol) at 20 °C for 1 h. After removal of the solvent by blowing a gentle stream of N_2, the residual liquid was dried under vacuum to a constant weight (3 g). Extensive decomposition happened during silica gel chromatography to separate and purify the cycloadducts **159a** and **160a**. As such, the crude products were silylated using the following procedure. To a solution of the crude adducts **159a** and **160a** (~10 mmol) in DMF (25 mL) was added imidazole (2.7 g, 40 mmol). A solution of t-butyldimethylsilyl chloride (2.1 g, 14 mmol) in DMF (10 mL) was added dropwise to the above mixture at 0°C over a period of 15 min. the reaction mixture, after stirring at 0 °C for 1 h, was allowed to warm to 20°C and stirring continued for an additional 4 h. The mixture was taken up in ether (50 ml) and washed with water (3×50 mL). The organic layer was dried over ($MgSO_4$), concentrated and the residual liquid was chromatographed over silica gel using hexane/ether as the eluent to give **159b** as a white solid. Continued elution afforded a mixture of **159b** and **160b**, and finally, the isomer **160b** as a coluorless liquid. The approximate ratio of **159b** and **160b** was found to be 3:1. The overall yield for the two steps was determined to be (3.18 g, 82%).

4.3.11.1. Major Diastereomer 159b

Both the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ revealed the presence of a single invertomer. Mp 45-46°C (ether/hexane); (Found: C, 55.7; H, 8.5; N, 3.6. $C_{18}H_{33}NO_6Si$ requires C, 55.79; H, 8.58; N, 3.61%.); ν_{max} (KBr) 2953, 2927, 2855, 1741, 1460, 1435, 1257, 12.05, 1104, 1005, 836, and 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.56 (1H, d, *J* 8.8 Hz, C2-$\underline{H}_aH_b$), 4.21 (1H, d, *J* 8.8 Hz, C2-$H_a\underline{H}_b$), 3.78 (3H, s, CO$\underline{Me}$), 3.77 (3H, s, CO$\underline{Me}$), 3.53-3.48 (1H, m, C3a-$\underline{H}$), 3.47-3.42 (2H, m, C$\underline{H}_2$OSi), 2.88 (1H, dd, *J* 2.4, 11.7 Hz, C7-$H_a\underline{H}_e$), 2.50 (1H, ddd, *J* 2.9, 9.5, 12.3 Hz, C7-$\underline{H}_aH_e$), 2.12 (1H, apparent d, *J* 13.1 Hz, C4-$\underline{H}_aH_b$), 1.83 (1H, apparent d, *J* 14.0 Hz, C6-$H_a\underline{H}_e$), 1.68-1.60 (1H, m, C5-$\underline{H}$), 1.41 (1H, dq, *J* 4.0, 12.5 Hz, C4-$H_a\underline{H}_b$), 1.03 (1H, q, *J* 11.9 Hz, C6-$\underline{H}_aH_e$), 0.87 (9H, s, C$\underline{Me}_3$), 0.031 (6H, s, $\underline{Me}_2$); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.2, 168.9, 71.8, 71.6, 67.0, 54.5, 53.3, 52.9, 52.8, 38.3, 29.3, 27.3, 25.9 (3C), 18.3, (-) 5.4 (2C).

4.3.11.2. Minor Diastereomer 160b

(Found: C, 55.6; H, 8.5; N, 3.5. $C_{18}H_{33}NO_6Si$ requires C, 55.79; H, 8.58; N, 3.61%.); The ^{13}C NMR spectrum revealed the presence of two invertomers in a 84:16. ν_{max} (neat) 2954, 2928, 2855, 1766, 1754, 1746, 1738, 1731, 1470, 1462, 1454, 1434, 1251, 1203, 1135, 1108, 1083, 1044, 1005, 837, and 776 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 3.28-3.83 (10H, m, including several $CO_2\underline{Me}$ singlets), 2.30-2.90 (2H, m), 1.50-2.03 (5H, m), 0.87 (9H, s, C$\underline{Me}_3$), 1.29-1.15 (1H, m, C6-$\underline{H}_aH_e$), 0.034 (3H, s, $\underline{Me}$), 0.031 (3H, s, $\underline{Me}$).

4.3.11.2.1. Major invertomer of 160b

δ_C (500 MHz, $CDCl_3$, +25 °C) 170.3, 168.9, 87.0, 67.1, 60.3, 53.3 (2C), 50.9, 38.1, 32.7, 27.7, 27.6, 25.9 (3C), 18.3, (-) 5.4 (2C).

4.3.11.2.2. Minor invertomer of 160b

δ_C (500 MHz, $CDCl_3$, +25 °C) 170.3, 168.9, 83.3, 63.5, 61.7, 53.3, 52.7, 51.4, 42.7, 33.3, 29.5, 25.9 (3C), 25.3, 18.3, (-) 5.4 (2C).

4.3.12. Thermolysis of 159b in toluene-d_6

A solution of the adduct **159b** (20 mg) in toluene-d_6 was thermolyzed at 90°C. After 30 min of heating the ratio of **159b** and **160b** became 77:23, while the ratio became72:28 after 2 h at 90°C and thereafter remained unchanged. The CO_2Me of **159b** appeared at δ3.29 and 3.35 ppm, while that of **160b** appeared at 3.32 and 3.39 ppm. The C(3a) proton of the **160b** appeared at δ3.70, while the C(2) Hs appeared at 4.83 (1H, d, *J* 8.6 Hz), 4.20 (1H, *J* 8.6 Hz).

4.3.13. Thermolysis of 159b in toluene in the presence of styrene (141b)

A solution of **159b** (400 mg, 1.03 mmol), styrene (1.5 mL) in toluene (5 mL) was stirred under N_2 at 100°C overnight. After removal of the solvent and excess alkene, residual liquid was chromatographed over silica gel using hexane/ether as the eluent to give **163** as a white solid. Continued elution afforded a mixture of **163-165**. The yield was found to be 83% (0.297 g). The crude mixture revealed the presence of three adducts as revealed by the presence of C(2)H of **162** at δ5.40 (major invertomer) and 5.02 (minor invertomer), **164** at 5.23 (1H, t, J 8.7 Hz, major invertomer) and 5.10 (minor invertomer, overlapping), and **165** at 5.10.

In order to determine the structure and composition of **163-165**, a portion of the above crude adducts was hydrolyzed with 5:1 MeOH/HCl at 20°C (10 min) to **142b-145b**. ^1H NMR ($CDCl_3$, -30°C) analysis of the crude hydrolyzed products revealed the presence

of three isomers **142b-144b,** hence **163-165,** in a ratio of 94:3:3 as indicated by integration of the C(2)H signals as described (Section 4.3.5).

4.3.13.1. Major adduct 163

Mp. 80-81°C (ether-pentane); (Found: C, 68.9; H, 9.4; N, 3.9. $C_{20}H_{33}NO_2Si$ requires C, 69.11; H, 9.57; N, 4.03%.); ν_{max} (KBr) 2928, 2888, 2855, 1459, 1386, 1361, 1253, 1115, 1077, 1044, 1006, 834, 763, 703 and 661 cm^{-1}. The major and minor invertomer at 25 °C was found to be in a ratio of 86:14 as determined by integration of the C(2)H. (The ratio becomes 93:7 at -40 °C).

4.3.13.1.1. Major invertomer 163

δ_H (500 MHz, $CDCl_3$, 25 °C) 7.37-7.25 (5H, m, Ph), 5.40 (1H, dd, *J* 3.6, 9.8 Hz, C2-H), 3.85-3.75 (1H, m, C3a-H), 3.51-3.41 (2H, m, CH_2OSi), 3.26-3.20 (1H, m, C7-H_aH_e), 2.83 (1H, ddd, *J* 2.6, 10.4, 13.1 Hz, C7-H_aH_e), 2.73 (1H, dt, *J* 10.0, 11.9 Hz, C3-H_aH_b), 1.50-2.00 (5H, m, C3-H_aH_b, C4-H_2, C5-H, C6-H_aH_e), 1.32-1.20 (1H, m, C6-H_aH_e), 0.89 (9H, s, CMe_3), 0.03 (6H, s, Me_2); δ_C (500 MHz, $CDCl_3$, 25 °C) -5.4 (2C), 18.3, 25.9 (3C), 27.7, 28.3, 32.7, 38.9, 49.5, 60.0, 67.5, 78.8, 126.4 (2C), 127.5, 128.4 (2C), 142.5.

4.3.13.1.2. Minor invertomer 163

δ_H(500 MHz, $CDCl_3$, 25°C). Minor invertomer has the following non-overlapping signals: δ5.02 (1H, dd, *J* 4.3 and 9.0 Hz, , C2-H, broad dd at 25°C became sharp at -40°C), 3.58-3.52 (1H, m, C3a-H), 3.33-3.27 (2H, m); δ_C (500 MHz, $CDCl_3$, 25 °C) 142.3, 128.4 (2C), 127.6, 126.8 (2C), 77.7, 63.8, 61.9, 51.2, 43.3, 33.8, 30.2, 25.6, 25.9 (3C), 15.0, -5.4 (2C).

4.3.14. Conversion 142a into its acetate 168a

The cycloadduct **142a** (1.28 g, 6.0 mmol) in CH_2Cl_2 (10 mL) was treated with acetic anhydride (3 mL) at 25 ºC for overnight. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chraomatography over silica gel using ether as eluant to give **168a** as a colourless liquid (1.46 g, 95%). (Found: C, 65.9; H, 9.8; N, 5.4. $C_{14}H_{25}NO_3$ requires C, 65.85; H, 9.87; N, 5.49 %.); $\square_{max}$ (neat) 2955, 2929, 2857,1742,1454, 1366, 1244, 1036, and 963 cm^{-1}. The ^1H NMR spectrum revealed the presence of two invertomers in a ratio of 83:17.

4.3.14.1. Major invertomer of 168a

δ_H (500 MHz, $CDCl_3$, +25 °C) 4.43-4.37 (1H, m, C2-H), 3.92 (2H, ABX, *J* 6.4, 10.7 Hz, CH_2OAc), 3.60 (1H, app. quint, *J* 5.8 Hz, C3a-H), 3.11 (1H, td, *J* 3.4, 10.4 Hz, C7-H_aH_e), 2.69 (1H, ddd, *J* 2.6, 10.4, 12.9 Hz, C7-H_aH_e), 2.33 (1H, dt, *J* 9.4, 11.9 Hz, C3-H_aH_b), 2.06 (3H, s, COMe), 2.00-1.80 (2H, m, C3-H_aH_b, C5-H), 1.78-1.68 (2H, m, C4-H_aH_e, C6-H_aH_e), 1.63-1.53 (1H, m, C4-H_aH_e), 1.55-1.45 (1H, m, C6-H_aH_e), 1.43-1.23 (6H, m, $(CH_2)_3Me$), 0.90 (3H, t, *J* 7.0 Hz, Me); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.0, 77.3, 68.3, 59.1, 48.8, 35.3, 35.2, 29.5, 28.3, 28.1, 27.6, 22.7, 20.9, 14.0.

4.3.14.2. Minor invertomer of 168a

δ_H ($CDCl_3$, +25 °C) Non overlapping signals at 4.13-4.09 (2H, m, CH_2OAc), 4.06-4.01 (1H, m, C2-H), 3.32-3.26 (1H, m, C3a-H) , 2.62-2.54 (1H, m), 2.03 (3H, s, COMe); δ_C (500 MHz, $CDCl_3$, +25 °C) 173.8, 76.1, 65.0, 61.0, 50.7, 40.0, 34.9, 30.5, 30.4, 28.0, 25.8, 22.7, 21.1, 4.0.

4.3.15. Conversion 142b into its acetate 168b

The cycloadduct **142b** (1.40 g, 6.00 mmol) in toluene (10 mL) was treated with acetic anhydride (1 mL) at 70ºC for 3 h. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using 60:40 hexane/ether as eluant to give **168b** as white crystals (1.58 g, 96%). Mp 97-98 °C (hexane/ther); *m/z* 275 [M^+]; (Found: C, 69.6; H,7.6; N, 5.0. $C_{16}H_{21}NO_3$ requires C, 69.79; H, 7.69; N, 5.09 %.); ν_{max} (KBr) 3028, 2952, 2919, 2854, 1741, 1456, 1366, 1245, 1035, 946, 903, 765, 708, 670, and 644 cm^{-1}. The major and minor invertomers of **168b** at 25 °C was found to be in a ratio of 88:12 as determined by integration of the C(2)H.

4.3.15.1. Major invertomer of 168b

δ_H (500 MHz, $CDCl_3$, 25 °C) 7.37-7.25 (5H, m, Ph) , 5.41 (1H, dd, J 3.7 and 9.8 Hz, C2-H) , 3.95 (2H, ABX, *J* 6.1, 6.4, 10.7Hz, CH_2OAc), 3.88-3.83 (1H, m, C3a-H), 3.24 (1H, td, *J* 3.4, 10.4 Hz, C7-H_aH_e) , 2.84 (1H, ddd, *J* 2.5, 10.4, 12.8 Hz, C7-H_aH_e), 2.73 (1H, app. q, *J* 11.6 Hz, C3-H_aH_b), 2.07 (3H, s, COMe), 1.75-2.15 (5H, m, C3-H_aH_b, C4-H_2, C5-H, C6-H_aH_e), 1.40 (1H, dq, *J* 2.2, 12,2 Hz, C6-H_aH_e); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.0, , 145.2 , 128.5 (2C) , 127.6, 126.4 (2C) , 78.8, 68.2, 59.7, 49.1, 38.8, 29.6, 28.3,27.6, 20.9.

4.3.15.2. Minor invertomer of 168b

Minor invertomer has the following non-overlapping signals: δ_H (500 MHz, $CDCl_3$, 25 °C) 5.02 (1H, dd, *J* 3.9 and 8.8 Hz, C2-H), 4.14 (2H, d, *J* 7.9 Hz, CH_2OAc), 3.42-3.37 (1H, m, C3a-H), 2.67-2.57 (1H, m), 2.33 (1H, app q, *J* 10.4 Hz), 1.74-1.65 (1H, m); δ_C (500 MHz, $CDCl_3$, 25 °C) 171.0, 141.5, 128.5 (2C), 127.9, 126.7 (2C), 77.7, 64.9, 61.6, 50.9, 43.1, 30.5 (2C), 25.9, 20.9.

4.3.16. MCPBA oxidation of adduct 168a to nitrones 169a and 170a. Cycloaddition of 169a with 1-hexene (141a)

To a stirred solution of the cycloadduct **168a** (3.0 mmol) in dichloromethane (30 mL) at 20ºC was added MCPBA (3.0 mmol) in one portion. After 30 m at 20 ºC the organic layer was washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers was dried (Na_2SO_4), concentrated to give a mixture of the aldonitrone **169a** and keto-nitrone **170a** in a ratio of 80:20, respectively, as a pale yellow liquid in almost quantitative yield. A small portion of the solution was concentarated for ^{1}H NMR analysis which revealed the aldonitrone **169a** having the following characteristic signals at δ7.18 (1H, t, *J* 3.5 Hz, CH=N), 4.24 (1H, m, =NCH), 2.08 (3H, s), 0.90 (3H, t, *J* 7.0 Hz). The Ketonitrone **170a** has the following nonoverlapping signals at δ3.00 (1H, dd, J 9.6, 13.1 Hz), 2.17 (3H, s).

After exchanging CH_2Cl_2 with toluene (15 mL), the above solution of nitrones was treated with 1-hexene (**141a**) (5 mL) at 75ºC for 48 h. After removal of the solvent and excess alkene, the residual mixture was separated by chraomatography over silica gel using 1:1 hexane/ether as eluant to give the minor cycloadduct **173a** as a colourless liquid (220 mg, 21%). Continued elution afforded the major isomer **172a** also as a colourless liquid (423 mg, 40%). Finally, elution with 90:10 ether/methanol afforded the unreacted ketonitrone **170a** as a colourless liquid.

4.3.16.1. Major cycloadduct 172a

(Found: C, 67.3; H, 10.2; N, 3.8. $C_{20}H_{37}NO_4$ requires C, 67.57; H, 10.49; N, 3.94%.); ν_{max} (neat) 3440, 2918, 2850, 1743, 1467, 1451, 1427, 1371, 1254, 1121, 1039, 901, 782, and 732 cm^{-1}. The ratio of the invertomers by ^{13}C was estimated to be 85:15.

4.3.16.1.1. Major invertomer of 172a

δH (500 MHz, $CDCl_3$, -40°C) 5.48 (1H, br s, O<u>H</u>), 4.13-4.05 (1H, m, C2-<u>H</u>), 3.95-3.83 (2H, m, C<u>H</u>$_2$OAc), 3.85-3.78 (1H, m, C3a-<u>H</u>), 3.74-3.66 (1H, m, C7-CH_2C<u>H</u>O), 3.57-3.49 (1H. m, C7-<u>H</u>), 2.10 (3H, s, CO<u>Me</u>), 1.10-2.05 (21H, m), 0.91 (6H, two overlapping t, *J* 7.0 Hz, CH_2<u>Me</u>, CH_2<u>Me</u>); δ_C (500 MHz, $CDCl_3$, -40°C) 171.7, 75.3, 70.0, 68.6, 54.2, 53.0, 40.9, 36.3, 35.9 (2C), 29.0, 28.6, 28.5, 28.1, 26.9, 22.8, 22.6, 21.2, 14.3, 14.2.

4.3.16.1.2. Minor invertomer of 172a

Minor invertomer has the following nonoverlapping signals: δ_C (500 MHz, $CDCl_3$, -40°C) 76.2, 68.0, 54.5, 39.3, 36.8, 34.9, 33.5, 32.8, 32.5, 30.3, 30.0, 27.9, 22.7.

4.3.16.2. Minor cycloadduct 173a

The ^1H spectrum revealed the presence of a single invertomer. (Found: C, 67.4; H, 10.3; N, 3.8. $C_{20}H_{37}NO_4$ requires C, 67.57; H, 10.49; N, 3.94 %.); ν_{max} (neat) 3430, 2954, 2927, 2858, 1742, 1466, 1451, 1433, 1370, 1237, 1036, 788 and 733 cm^{-1}; δ_H (500 MHz, $CDCl_3$, 25 °C) 3.80-4.15 (4H, m, C2-<u>H,</u> C<u>H</u>$_2$OAc, C3a-<u>H</u>), 2.98-2.90 (1H, m, C7-<u>H</u>), 2.48-2.36 (1H. m, C3-<u>H</u>$_a$H$_b$), 2.05 (3H, s, CO<u>Me</u>), 1.20-2.00 (21H, m), 0.90 (6H, two overlapping t, *J* 7.0 Hz, CH_2<u>Me</u>, CH_2<u>Me</u>); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.1, 75.9,

68.4, 65.2, 61.0, 58.4, 40.1, 39.8, 37.4, 34.8, 31.3, 31.2, 29.9, 27.9 (2C), 22.7, 22.6, 20.9, 14.1, 14.0.

4.3.16.3. ketonitrone 170a

(Found: C, 61.7; H, 9.4; N, 5.2. $C_{14}H_{25}NO_4$ requires C, 61.97; H, 9.29; N, 5.16%.); ν_{max} (neat) 3366, 2955, 2929, 2858, 1738, 1446, 1367, 1245, 1193, 1150, and 1041 cm^{-1}, δ_H (500 MHz, $CDCl_3$, +25 °C) 6.13 (1H, Br O<u>H</u>), 4.05 (2H, app. d, *J* 6.1 Hz, C<u>H</u>$_2$OAc), 3.96 (1H, m, C<u>H</u>OH), 3.96-3.84 (2H, m, C6-<u>H</u>$_2$), 3.04 (1H, dd, *J* 9.7, 12.9 Hz, C6-C<u>H</u>$_a$H$_b$CHOH), 2.73-2.57 (1H, m, C6-CH$_a$<u>H</u>$_b$CHOH), 2.36 (1H, app d, *J* 11.9 Hz, C3-<u>H</u>$_a$H$_b$), 2.28-2.20 (1H, m, C3-H$_a$<u>H</u>$_b$), 2.09 (3H, s, CO<u>Me</u>), 1.20-1.90 (9H, m), 0.91 (3H, t, *J* 6.7 Hz, <u>Me</u>); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.8, 148.5, 71.8, 66.5, 57.0, 40.0, 38.4, 33.6, 30.0, 27.7, 25.7, 22.7, 20.8, 14.1.

4.3.17. MCPBA oxidation of adduct 168a to nitrones 169a and 170a. Cycloaddition of 169a with methyl methacrylate (153)

The mixture of nitrones **169a** and **170a** (prepared by MCPBA oxidation of **168a** (1.0 mmol) as described in Section 4.3.16) in CH_2Cl_2 (10 mL) was treated with methyl methacrylate (1.0 mL) and the mixture was stirred at 20ºC for overnight. The ketonitrone was unreactive under these conditions. After removal of the solvent and excess alkene, the residual liquid was separated by chromatography over silica gel using 97:3 ether/methanol as eluant to give the first fraction as a nonseparable mixture of three isomers as a colorless liquid (48 mg, 8.7%). Continued elution gave the second fraction containing the major adduct **176** as a colourless liquid (353 mg, 63%). Analysis of the first fraction revealed the presence three isomers as indicated by the ^{1}H NMR spectrum which displayed C(2) methyl

singlets at δ1.45**,** 1.46 and 1,49 ppm in an approximate ratio of 1.5:1:1. The acetyl singlets appeared at 2.01, 2.02 and 2.03 ppm and the CO_2Me singlets appeared at 3.71, 3.74 and 3.75 ppm**.** The ratio of **176** and the combined minor isomers was thus found to be 88:12.

4.3.17.1. Major adduct 176

(Found: C, 61.3; H, 8.9; N, 3.7. $C_{19}H_{33}NO_6$ requires C, 61.43; H, 8.95; N, 3.77%.); ν_{max} (neat) 3445, 2953, 2931, 2858, 1742, 1738, 1732, 1462, 1454, 1446, 1434, 1371, 1242, 1150, 1121, 1038 and 982 cm^{-1}. The major and minor invertomers of **176** at -40 ºC was found to be in a ratio of 72:28 as determined by integration of several proton signals.

4.3.17.1.1. Major Invertomer of 176

δ_H (500 MHz, $CDCl_3$, -40 °C) 5.00 (1H, Br O<u>H</u>), 3.82 (3H, s, CO_2<u>Me</u>), 3.96-3.78 (4H, m, C<u>H</u>$_2$OAc, C7-CH$_2$C<u>H</u>O, C3a-<u>H</u>), 3.65-3.55 (1H, m, C7-<u>H</u>), 2.11 (3H, s, CO<u>Me</u>), 1.90-2.50 (5H, m), 1.50 (3H, s, C2-<u>Me</u>), 1.00-1.75 (10H, m), 0.91 (3H, t, *J* 6.7 Hz, CH$_2$<u>Me</u>); δ_C (500 MHz, $CDCl_3$, -40 °C) 173.8, 171.5, 80.5, 70.0, 68.3, 54.7, 53.1 (2C), 45.7, 36.6, 35.9, 32.1, 28.9, 28.4, 27.2, 25.9, 22.8, 21.2, 14.3.

4.3.17.1.2. Minor Invertomer of 176

The ^{1}H NMR (500 MHz, $CDCl_3$, -40 °C) revealed the following nonoverlapping signals at: 3.79 (3H, s, CO_2<u>Me</u>) , 2.89-2,82 (1H, m), 2.09 (3H, s, CO<u>Me</u>), 1.42 (3H, s, C2-<u>Me</u>); δ_C (500 MHz, $CDCl_3$, -40 °C) 175.8, 171.5, 79.8, 71.2, 68.3, 56.2, 55.5, 53.1, 44.3, 37.8, 35.9, 31.2, 30.0, 28.4, 27.8, 24.7, 22.6, 21.2, 14.3.

4.3.18. MCPBA oxidation of adduct 168a to lactam 171a

To a stirred solution of the cycloadduct **168a** (128 mg, 0.5 mmol) in dichloromethane (10 mL) at -40ºC was added MCPBA (1.1 mmol) in one portion. The reaction mixture was then stirred 10 min each at -40ºC, -20ºC -0ºC and 20 min at 20ºC. The organic layer was then washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers was dried (Na_2SO_4), concentrated and the residual mixture was purified by chromatography over silica gel using 90:10 ether/methanol as eluant to give the lactam **171a** as a lquid (110 mg, 77%)**.** The crude spectrum revealed the presence of ketonitrone **170a** (~15%). However, the ketonitrone **170a** was not separated in this case. **171a:** *m/z* 288 [M^++*1*]; (Found: C, 58.4; H, 8.6; N, 4.8. $C_{14}H_{25}NO_5$ requires C, 58.52; H, 8.77; N, 4.87 %.); ν_{max} (KBr) 3380, 2954, 2930, 2870, 1743, 1642, 1632, 1468, 1454, 1416, 1371, 1315, 1246, 1046 and 731 cm^{-1}, δ_H (500 MHz, $CDCl_3$, +25 °C) 4.11-4.04 (1H, m, C6-H), 4.03-3.94 (2H, m, CH_2OAc), 3.92-3.84 (1H, m, C6-CH_2CHO), 2.57 (1H, dd, *J* 5.3, 17.2 Hz, C3-H_aH_e), 2.44-2.34 (1H, m, C6-CH_aH_bCHO), 2.23 (1H, dd, *J* 10.2, 17.2 Hz, C3-H_aH_e), 2.07 (3H, s, COMe), 1.99-1.90 (2H, m, C6-CH_aH_bCHO, C4-H), 1.89-1.78 (1H, m, C5-H_aH_e), 1.75-1.65 (1H, m, C5-H_aH_e), 1.54-1.28 (6H, m, $(CH_2)_3$), 0.91 (3H, t, *J* 7.0 Hz, Me); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.8, 163.7, 69.2, 66.6, 55.6, 41.2, 37.4, 33.6, 31.3, 28.5, 27.7, 22.6, 20.7,14.0.

4.3.19. MCPBA oxidation of adduct 168b to nitrones 169b and 170b. Cycloaddition of 169b with styrene (141b) to cycloadducts 172b and 173b

To a stirred solution of the cycloadduct **168b** (3.0 mmol) was oxidized with MCPBA using procedure as described in Section 3.16 to give in dichloromethane (30 mL)

at 20ºC was added MCPBA (3.0 mmol) in one portion. After 30 min at 20 ºC the organic layer was washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers were re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers was dried (Na_2SO_4), concentrated to give a mixture of the aldonitrone **169b** and keto-nitrone **170b** in a ratio of 82:18, respectively, as determined by ^{1}H NMR integration of several proton signals. A small portion of the solution was concentrated for ^{1}H NMR analysis which revealed the aldonitrone **169b** having the following characteristic signals at δ 7.19 (1H, t, *J* 3.5 Hz, CH=N), 4.09 (1H, m, =NCH), 2.06 (3H, s), 3.97 (2H, d, J 61 Hz, CH_2O), 5.05 (1H, dd, J 3.6, 7.4 Hz). The NMR spectra of the ketonitrone **170b** are described later.

After exchanging the solvent CH_2Cl_2 with toluene (15 mL), the above solution of nitrones was treated with styrene (**141b**) (5 mL) at 60ºC for 48 h. After removal of the solvent and excess alkene, the residual mixture was analysed by ^{1}H NMR analysis which revealed the presence of two cycloadducts **172b** and **173b** as well as the unreacted ketonitrone **170b.** The **172b**/**173b** was found to be in a ratio of 40:60 as determined by integration of several proton signals at δ 3.16 (1H, m, major **173b**), 4.15 (2H, AB, CH_2O, major **173b**), 3.90 (2H, d, CH_2O, minor **172b**). The crude mixture of adducts were purified by chromatography over silica gel using 3:2 hexane/ether as eluant to give a nonseparable mixture of the cycloadducts **172b** and **173b** (in a ratio of 40:60) as a colourless liquid (830 mg, 70%). TLC analysis in several solvents revealed the nonseparability of the adducts by silica gel chromatography. The adduct mixture was not analyzed further, instead it was hydrolyzed by NaOH to a separable mixture of isomers **174** and **175** (See section 4.3.20). Finally, elution with 80:20 ether/methanol afforded the unreacted ketonitrone **170b** as a white solid (122 mg, 14%).

4.3.19.1. ketonitrone 38b

Mp 98-99°C (CH_2Cl_2-pentane), *m/z* 274 [M^+-*OH*]; (Found: C, 65.8; H, 7.3; N, 4.7. $C_{16}H_{21}NO_4$ requires C, 65.96; H, 7.27; N, 4.81%.); ν_{max} (KBr) 3146, 2953, 2919, 2857, 1735, 1615, 1485, 1448, 1419, 1363, 1243, 1187, 1144, 1056, 1030, 990, 915, 882, 834, 766 and 709 cm^{-1}, δ_H (500 MHz, $CDCl_3$, +25 °C) 7.30 (6H, Ph, O<u>H</u>) , 5.17 (1H, dd, *J* 3.1, 8.0 Hz, PhC<u>H</u>O), 3.92-3.82 (4H, m, C<u>H</u>$_2$OAc, C6-<u>H</u>$_2$), 3.04 (1H, dd, *J* 2.2, 13.2 Hz, C2-C<u>H</u>$_a$H$_b$CHO), 2.94 (1H, dd, *J* 7.7, 13.2 Hz, C2-CH$_a$<u>H</u>$_b$CHO), 2.41 (1H, dd, *J* 5.5, 19.5 Hz, C3-<u>H</u>$_a$H$_b$), 2.13-2.03 (1H, m, C3-H$_a$<u>H</u>$_b$), 2.05 (3H, s, CO<u>Me</u>), 2.02-1.90 (1H, m, C4-<u>H</u>), 1.70 (1H, dd, *J* 9.7, 19.5 Hz, C5-<u>H</u>$_a$H$_b$),1.67-1.55 (1H, m, C5-H$_a$<u>H</u>$_b$); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.6, 148.1, 144.3, 128.3 (2C), 127.3, 125.1 (2C), 73.7, 66.1, 56.7, 42.6, 33.9, 29.6, 25.3, 20.7.

4.3.20. Conversion of 172b and 173b into 174 and 175 by hydrolysis with NaOH

A solution of **172b** and **173b**, in a ratio of 40:60, (800 mg, 2.02 mmol) in methanol (5 mL) containing NaOH (100 mg, 2.5 mmol) was stirred at 20 °C for 10 min. The reaction was over as indicated by TLC experiment (silica, ether). The reaction mixture was diluted with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers was dried (Na_2SO_4) and concentrated and the residual liquid was separated by chromatography over silica gel using ether as eluant to give **175** as a white solid (310 mg)**.** Continued elution gave a mixture of adducts **174** and **175** (132 mg) and finally the pure adduct **174** (200 mg). The total yield of the hydrolyzed adducts were found to be (642 mg, 90%). The ratio of the hydrolyzed adducts **174** and **175** were found to be similar to the

ratio of the starting acetylated adducts **172b** and **173b** as revealed by the ^{1}H NMR of the crude mixture.

4.3.20.1. Minor diasteromer 174

Colourless liquid; *m/z* 353 [M^{+}]; (Found: C, 74.5; H, 7.5; N, 3.9. $C_{22}H_{27}NO_3$ requires C, 74.76; H, 7.70; N, 3.96%.); ν_{max} (neat) 3354, 3062, 3030, 2919, 1603, 1493, 1452, 1367, 1307, 1043, 952, 911, 858, 788, 700 cm^{-1}. The major and minor invertomers of **174** at -40°C was found to be in a ratio of 87:13 as determined by integration of the benzylic proton signals.

4.3.20.1.1. Major invertomer of 174

δH (500 MHz, $CDCl_3$, -40 °C) 7.37-7.21 (10H, m, Ph, Ph) , 6.75 (1H, br, O<u>H</u>), 5.12-5.06 (2H, m, C2-<u>H</u>, PhC<u>H</u>OH), 3.75-3.65 (1H, m, C3a-<u>H</u>), 3.64-3.54 (1H, m, C7-<u>H</u>), 3.50-3.40 (2H, m, C<u>H</u>$_2$OH), 2.56-2.40 (4H, m, C3-H$_2$, C7-C<u>H</u>$_a$H$_b$CHO, O<u>H</u>), 1.92-1.80 (1H, m, C5-H), 1.74 (1H, apparent d, *J* 14.0 Hz, C7-CH$_a$<u>H</u>$_b$CHO), 1.63 (1H, apparent d, *J* 13.2 Hz, C4-H$_a$<u>H</u>$_e$), 1.55 (1H, dt, *J* 5.2, 13.2 Hz, C6-H$_a$<u>H</u>$_e$), 1.22 (1H, apparent q, *J* 12.2 Hz, C4-<u>H</u>$_a$H$_e$), 1.15 (1H, apparent d, *J* 12.2 Hz, C6-<u>H</u>$_a$H$_e$); δ_C (500 MHz, $CDCl_3$, -40 °C) 144.0, 143.3, 128.5 (2C), 128.2 (2C), 127.4, 126.6, 125.4 (2C), 125.3 (2C), 76.3, 72.2, 67.4, 54.9, 53.3, 44.4, 38.7, 32.1, 28.6, 26.6.

4.3.20.1.2. Minor invertomer of 174

Minor invertomer of **174** has the following nonoverlaping signals: δ_H (500 MHz, $CDCl_3$, -40 °C) 4.90 (1H, m, C2-<u>H</u>), 4.88-4.80 (1H, m, PhC<u>H</u>OH), 3.92-3.84 (2H, m, C3a-<u>H</u>, C7-<u>H</u>), 3.01-2.89 (2H, m, C3-<u>H</u>$_2$), 2.46-2.38 (1H, m, C7-C<u>H</u>$_a$H$_b$CHO), 2.30-2.20

(1H, m, C7-C<u>H</u>$_a$H$_b$CHO), 1.10-1.00 (1H, m, C6-<u>H</u>$_a$H$_e$); δ_C (500 MHz, $CDCl_3$, -40 °C) 73.8, 66.5, 57.0, 42.4, 33.3, 33.0.

4.3.20.2. Major diasteromer 175

m/z 353 [M^+]; mp 125-126 °C (ether-pentane). (Found: C, 74.8; H, 7.8; N, 3.9. $C_{22}H_{27}NO_3$ requires C, 74.76; H, 7.70; N, 3.96%.) ν_{max} (KBr) 3280, 3181, 3029, 2906, 1485, 1452, 1380, 1306, 1242, 1206, 1037, 910, 859, 799, 760, 699, 624, and 556 cm^{-1}. The ^1H spectrum revealed the presence of a single invertomer.δ_H (500 MHz, $CDCl_3$, 25 °C) 7.38-22 (10H, m, Ph, Ph), 5.11 (1H, dd, *J* 2.2, 10.2 Hz, C2-<u>H</u>), 5.07 (1H, dd, *J* 4.3, 9.5 Hz, PhC<u>H</u>OH), 4.36 (1H, br s, O<u>H</u>), 3.66 (2H, d, *J* 7.3 Hz, C<u>H$_2$</u>OH), 3.15-3.05 (1H, m, C7-<u>H</u>), 2.79-2.63 (1H, m, C3-<u>H$_a$H$_b$</u>), 2.35 (1H, apparent q, *J* 10.7 Hz, C3-H$_a$<u>H$_b$</u>), 1.70-2.30 (8H, m), 1.65 (1H, dt, *J* 5.1, 13.0 Hz, C6-<u>H$_a$</u>H$_e$); δ_C (500 MHz, $CDCl_3$, 25 °C) 144.8, 141.4, 128.5 (2C), 128.2 (2C), 127.8, 127.0, 126.6 (2C), 125.7 (2C), 77.4, 71.3, 63.6, 61.8, 59.0, 43.0, 42.7, 34.6, 31.2, 29.6.

4.3.21. MCPBA oxidation of adduct 168b to lactam 171b

The cycloadduct **168b** (0.5 mmol) was oxidized with MCPBA (1.1 mmol) using procedure as described in Section 3.18. Similar workup and chromatography afforded the lactam **171b** as a white solid (115 mg, 75%)**.** ^1H NMR revealed the presence of ketonitrone **168b** (~15%). Mp 96-97°C (ether)**;** *m/z* 307 [M^+]; (Found: C, 62.4; H, 6.7; N, 4.5. $C_{16}H_{21}NO_5$ requires C, 62.53; H, 6.89; N, 4.56%.); ν_{max} (KBr) 3136, 3025, 2942, 2922, 2883, 1740, 1622, 1492, 1454, 1418, 1365, 1342, 1243, 1225, 1181, 1123, 1085, 1045, 759, and 701 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 7.40-7.26 (5H, m, Ph), 5.03 (1H, d, *J* 6.5 Hz, PhC<u>H</u>O), 4.12-4.00 (1H, m, C6-<u>H</u>), 3.95 (2H, d, *J* 6.1 Hz, C<u>H$_2$</u>OAc), 2.56 (1H,

dd, *J* 5.0, 17.1 Hz, C3-$H_a\underline{H_e}$), 2.38-2.24 (1H, m, C6-C$\underline{H_a}H_b$CHO), 2.20 (1H, dd, *J* 10.4, 17.1 Hz, C3-$\underline{H_a}H_e$), 2.20 (1H, overlapping m, C6-C$\underline{H_a}H_b$CHO), 2.05 (3H, s, CO<u>Me</u>), 1.85-1.75 (2H, m, C<u>4</u>-H, C5-$\underline{H_a}H_e$), 1.45-1.35 (1H, m, C5-$\underline{H_a}H_e$); δ_C (500 MHz, $CDCl_3$, +25 °C) 170.8, 164.0, 144.2, 128.4 (2C), 127.4, 125.5 (2C), 71.51, 66.5, 55.8, 43.0, 33.6, 31.1, 28.2, 20.7.

4.3.22. Conversion of 172a to 177 by treatment with zinc and acetic acid

To a vigorously stirred solution of the adduct **172a** (0.3 mmol) in acetic acid (2 mL) and water (2 mL) at 60 °C was added Zn (0.85 g) in two portions (ca. 5 min). The reaction mixture was stirred at 60°C for a total 30 min. The reaction mixture was decanted and the residual solid was washed with water (10 mL) and CH_2Cl_2 (20 mL). After basification (K_2CO_3), the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried (Na_2SO_4), concentrated to give the amine **177** in almost quantitative yield as a solid. Mp 75-76°C (ether); (Found: C, 66.9; H, 10.8; N, 3.8. $C_{20}H_{39}NO_4$ requires C, 67.19; H, 10.99; N, 3.92%.); ν_{max} (neat) 3313, 2929, 2858, 1742, 1574, 1433, 1454, 1368, 1243, 1127, 1092, 1037, and 732 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.0-3.0 (3H, br, N<u>H</u>, O<u>H</u>, O<u>H</u>), 3.90 (1H, dd, BX of a ABX, *J* 6.1, 11.0 Hz, C$\underline{H_a}H_b$OAc), 3.85 (1H, dd, AX of a ABX, *J* 6.4, 11.0 Hz, $CH_a\underline{H_b}$OAc), 3.82-3.80 (2H, m, C<u>H</u>OH, C<u>H</u>OH), 3.59-3.47 (1H, m, C2-<u>H</u>), 3.21-3.08 (1H, m, C6-<u>H</u>), 2.20-2.10 (1H, m, C4-<u>H</u>), 2.08 (3H, s, CO<u>Me</u>), 1.20-1.70 (20H, m), 0.90 (6H, two overlapping triplets, *J* 7.0 Hz, <u>Me</u>, <u>Me</u>); δ_C (500 MHz, $CDCl_3$, +25 °C) 171.1, 69.8, 69.2, 68.2, 47.9, 45.6, 42.8, 37.4, 37.0, 36.2, 35.1, 34.0, 30.9, 28.3, 28.1, 22.8 (2C), 20.9,14.1 (2C).

4.3.23. Conversion of 173a to 178 by treatment with zinc and acetic acid

Using procedure as described in Section 4.3.22, the adduct **173a** was converted into **178** as a solid in 95% yield. Mp 64-65°C (ether); (Found: C, 66.9; H, 11.2; N, 4.0; $C_{20}H_{39}NO_4$ requires C, 67.19; H, 10.99; N, 3.92 %.) ν_{max} (neat) 3351, 2928, 2858, 1742, 1645, 1632, 1573, 1555, 1452, 1370, 1246, 1128, and 1037 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.18 (2H,d, *J* 7.9 Hz, C<u>H</u>$_2$OAc), 3.83-3.73 (2H, m, C<u>H</u>OH, C<u>H</u>OH), 3.06-2.94 (2H, m, C2-<u>H</u>, C6-<u>H</u>), 2.20-2.10 (1H, m, C4-<u>H</u>), 2.07 (3H, s, CO<u>Me</u>), 1.20-1.60 (23H, m), 0.90 (6H, t, *J* 6.8 Hz, <u>Me</u>, <u>Me</u>); δ_C ($CDCl_3$, +25 °C) 171.2, 68.5 (2C), 65.3, 48.5 (2C), 42.8 (2C), 37.7 (2C), 32.5 (2C), 31.5, 28.0 (2C), 22.7 (2C), 21.0, 14.1 (2C).

4.3.24. Conversion of 174 to 179 by treatment with zinc and acetic acid

Using procedure as described in Section 4.3.22, the adduct **174** was converted into **179** as a solid in 95% yield. In the work up procedure, the aqueous layer was extracted with hot $CHCl_3$ instead of CH_2Cl_2 (as a result of poor solubility of the product). Mp 146-148°C (ether); (Found: C, 74.1; H, 8.1; N, 3.8. $C_{22}H_{29}NO_3$ requires C, 74.33; H, 8.22; N, 3.94%.); ν_{max} (KBr) 3320, 3054, 3020, 2928, 2907, 2853, 1490, 1448, 1365, 1351, 1218, 1144, 1115, 1094, 1067, 1022, 914, 881, 853, 786, 760, 749, and 701 cm^{-1}; δ_H (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 7.37-7.24 (10H, m, Ph, Ph), 4.94 (1H, dd, *J* 3.4, 8.6 Hz, PhC<u>H</u>OH), 4.98 (1H, dd, *J* 4.3, 6.1 Hz, PhC<u>H</u>OH), 3.35 (3H, a two proton d, *J* 6.1 Hz, C<u>H</u>$_2$OH, and an overlapping 1H, m, C2-H), 3.19-3.11 (1H, m, C6-H), 2.71 (4H, br, O<u>H</u>s, N<u>H</u>), 2.37 (1H, ddd, *J* 4.2, 10.4, 14.6 Hz, C2-C<u>H</u>$_a$H$_b$CHO), 1.90-1.75 (2H, m C2-CH$_a$<u>H</u>$_b$CHO, C6-C<u>H</u>$_a$H$_b$CHO), 1.72-1.65 (2H, m, C6-CH$_a$<u>H</u>$_b$CHO, C4-<u>H</u>), 1.59-1.53 (1H, m, C5-C<u>H</u>$_a$H$_b$), 1.51-1.47 (1H, m C5-CH$_a$<u>H</u>$_b$), 1.18 (1H, dt, *J* 5.5, 12.8 Hz, C3-C<u>H</u>$_a$H$_b$), 0.83 (1H, q, *J* 12.5 Hz, C3-H$_a$<u>H</u>$_b$); δ_C (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25°C) 145.1, 144.9,

128.4 (2C), 128.4 (2C), 127.1, 127.1, 125.6 (2C), 125.6 (2C), 72.1, 70.5, 67.8, 48.2, 45.8, 45.3, 37.7, 36.2, 33.9 (2C).

4.3.25. Conversion of 175 to 180 by treatment with zinc and acetic acid

Using procedure as described in Section 4.3.22, the adduct **175** was converted into **180** as a solid in 90% yield. In the work up procedure, the aqueous layer was extracted with hot $CHCl_3$ instead of CH_2Cl_2 (as a result of poor solubility of the product). Mp 199-200°C (ether); (Found: C, 74.2; H, 8.0; N, 3.9. $C_{22}H_{29}NO_3$ requires C, 74.33; H, 8.22; N, 3.94%.); ν_{max} (KBr) 3311, 3171, 2931, 2884, 2718, 1450, 1388, 1332, 1262, 1205, 1119, 1063, 1037, 987, 914, 878, 827, 788, 759, and 702 cm^{-1}; δ_H (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 7.38-7.32 (10H, m, Ph, Ph), 4.88 (2H, dd, *J* 4.3, 8.0 Hz, PhC<u>H</u>OH, PhC<u>H</u>OH), 4.00 (4H, br s, OHs and NH), 3.55 (2H, d, *J* 7.6 Hz, C<u>H</u>$_2$OH), 2.95-2.82 (2H, m, C2-H, C6-H), 2.08-2.00 (1H, m, C4-<u>H</u>), 1.72-1.68 (4H, m, C3-C<u>H</u>$_2$CHO, C6-C<u>H</u>$_2$CHO,), 1.64 (2H, apparent d, *J* 13.5 Hz, C3-H$_a$<u>H</u>$_e$, C5-H$_a$<u>H</u>$_e$), 1.41 (2H, dt, *J* 5.2, 13.5 Hz, C3-<u>H</u>$_a$H$_e$, C5-<u>H</u>$_a$H$_e$); δ_C (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 144.5 (2C), 128.1 (4C), 127.0 (2C), 125.4 (4C), 70.8 (2C), 62.7, 48.1 (2C), 44.7 (2C), 34.4, 32.6 (2C).

CHAPTER 5

Regioselective transformation of 6/5-fused bicyclic isoxazolidines to second-generation cyclic aldonitrones

Summary:

The cycloaddition reactions of 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide with mono- and di-substituted alkenes have been found to be highly stereo- as well as face-selective. In solution, the 6/5 fused bicyclic cycloadducts remain solely as the *cis*-fused invertomers in order to accommodate the bulky tertiary substituent 2-hydroxy-2-propyl in the equatorial orientation. The cycloadducts, upon peracid oxidation, leads to the exclusive formation of synthetically important second-generation cyclic aldonitrones. The stereo- and face-selectivity of the cycloaddition reactions of these second-generation nitrones bearing substituents at C(4) and C(6) have been briefly examined.

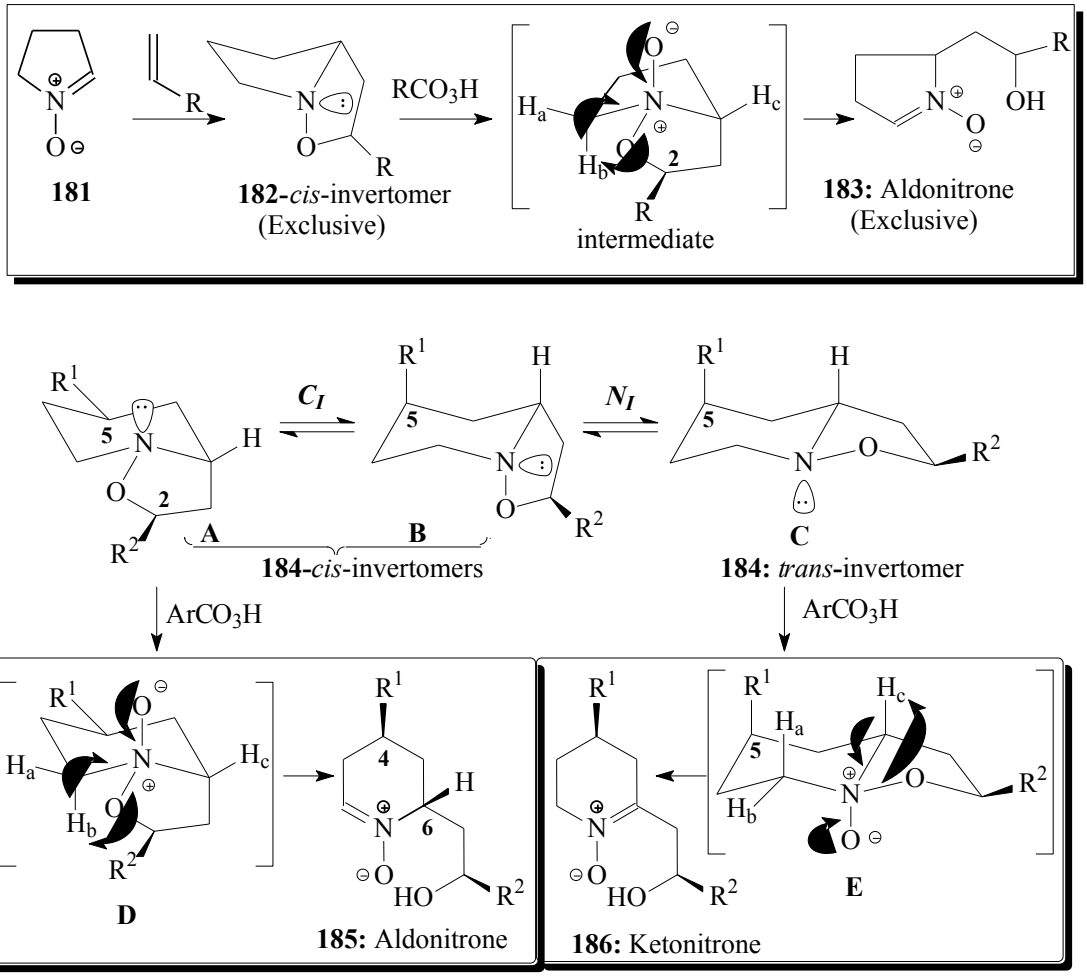
5.1 Introduction

The efficacy of 1,3-Dipolar cycloaddition reaction of cyclic nitrones lies on the remarkable selectivity in the incorporation of multiple stereocenters in a single step [1,2]. The pyrrolidine- and piperidine-based alkaloids, which are widespread in nature, can be accessed through the cycloaddition reaction of the parent five- **181** and six-membered cyclic nitrones, or the second-generation aldonitrones **183** and **184**, respectively (Scheme 50) [89]. The five-membered aldonitrones **183** can be accessed regiospecfically by peracid-induced ring opening of the bicyclic isoxzolidines **181** (nitrone (1)-alkene cycloaddition products). It has been suggested that the orientation of the nitrogen lone pair in **182** dictates the formation of the N-oxide intermediate on the β-face of the nitrone; the

subsequent ring opening leads the C(2)-O- to abstract the nearby H_b immediately, thereby leading to the exclusive formation of the aldonitrones**183** [77a]. However, the proper utilization of the second-generation six-membered aldonitrones **185** has been severely hampered by the lack of selectivity for the oxidation process in 6/5-fused isoxazolidines **184a,b** (R_1=H) (Table in Scheme 1), where the synthetically less important ketonitrones **186a,b** are obtained as the major products. While the geometric compulsion makes sure that the 5/5-ring system in **182** remains *cis*-fused, it's corresponding 6/5 ring system in cycloadducts **184** exists in three different conformations/configurations: the *cis* pair **A** and **B**, in rapid equilibrium by chair inversion (**CI**), and its *trans* invertomer **C**, in a relatively slow equilibrium with cis invertomer **B** by nitrogen inversion process (**NI**). It has been suggested that the higher activation barrier to nitrogen inversion ($\Delta G^{\#}$, ~70 kJ/mol) [90a] than the oxidation process does not permit the Curtin-Hammett principle[91] to apply; as such the invertomer ratio reflects the ratio of the products keto- and aldo-nitrones. While the cis invertomer leads to aldonitrones **185** *via* intermediate **D**, the trans invertomer affords the synthetically less important ketonitrones **186** *via* **E**. As evident from the Table included in the Scheme 48, the cycloadduct **184a** having a *cis/trans* invertomer ratio of 24:76 afforded the aldo-**185**/keto-**186** nitrones in an almost identical ratio of 23:77.9 Likewise, **184b** having a *cis/trans* invertomer ratio of 22:78 affords the aldo-**185**/keto-**186** nitrones in a similar ratio of 35:65 [7a].

Note that the placement of a substituent R1 at C(5) in cycloadducts **184** would favour the *cis* invertomer **A** at the expense of **B** and the trans invertomer **C**, both of which places the C(5)R_1 in the unfavourable axial orientation. Exploring this idea, greater percentages of the aldonitrones **185** are obtained from peracid-induced oxidation of the

isoxazolidines **184c** and **184d** [73,97]. In our continuing endeavour to obtain the aldonitrones **185** regiospecifically, we intended to place at C(5) in **184** a very bulky substituent that would ascertain the exclusive presence of the invertomer **A** and exclude the C(5) axially-oriented R_1 in cis **B** and trans invertomer **C**. The current work describes our attempt to test the above proposition and confirm the mechanism of the peracid oxidation process.



184	% Composition of invertomers *(cis/trans)*	% Composition of nitrones *(aldo-**185**/keto-**186**)*
a, $R^1 = R^2 = H$	24:76	23:77
b, $R^1 = H$; $R^2 = Ph$	22:78	35:65
c, $R^1 = CO_2Bu$; $R^2 = Ph$	55:45	52:48
d, $R^1 = CH_2OAc$; $R^2 = Ph$	88:12	82:18

Scheme 50.

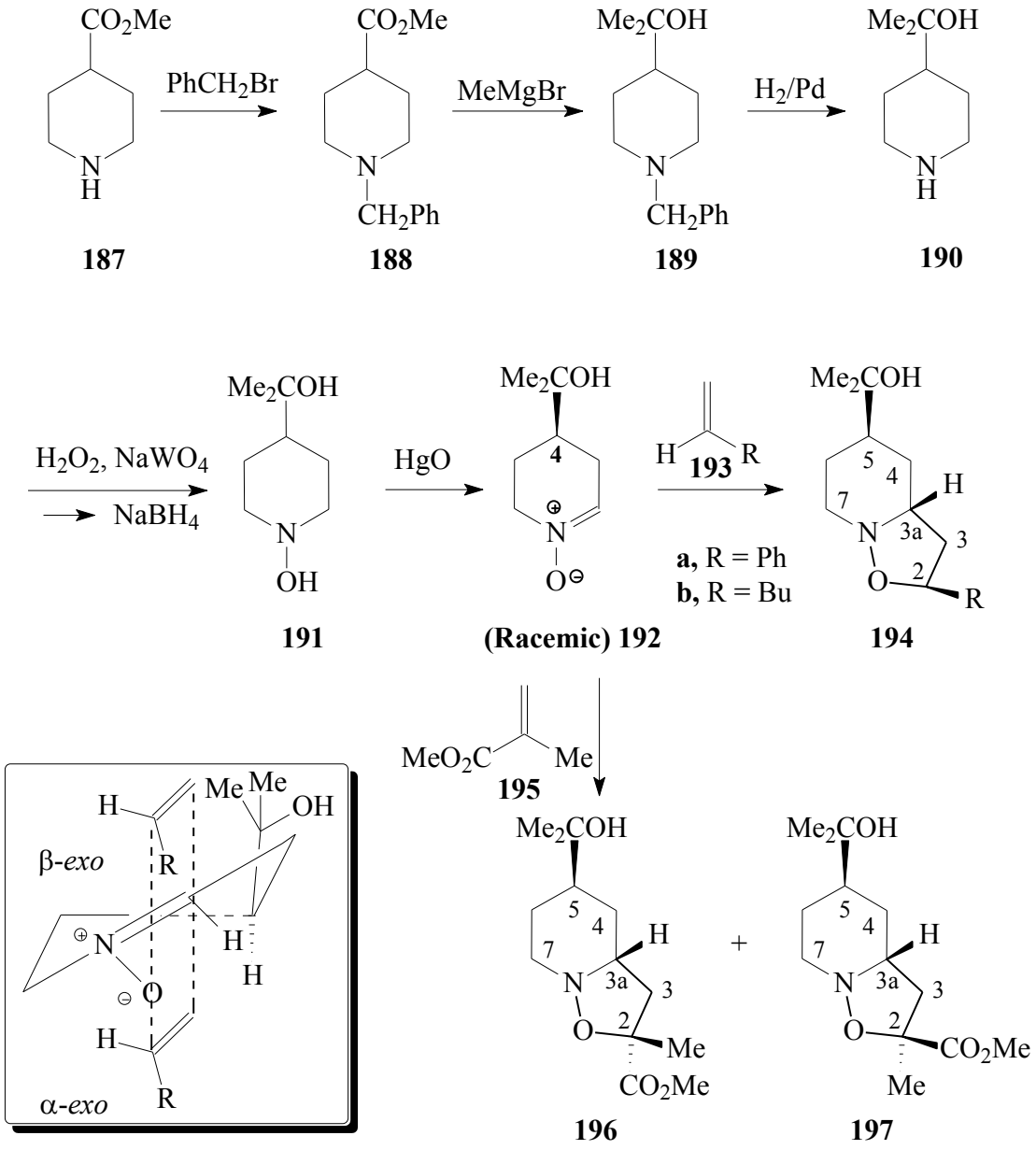
5.2 Results and Discussion

The synthesis of nitrone **192**, having a bulky CMe_2OH at C(4) is outlined in (Scheme 51). Amine **190** upon hydrogen peroxide oxidation in the presence of sodium tungstate[96] in water afforded a mixture of nitrone **192** and hydroxylamine **191** which upon treatment with $NaBH_4$ afforded the hydroxylamine **191** in pure form. The required nitrone **192** was then prepared by mercury(II) oxide oxidation of **191**.

Next, we pursued the addition reaction of nitrone **192** with various alkenes. The addition of monosubstituted alkene styrene **193a** was found to be stereo-, as well as face-selective; a single adduct **194a** was obtained in 80% yield. The ^1H NMR analysis of the crude as well as purified product failed to reveal the presence of any minor isomer. Likewise, the addition reaction of 1-hexene **193b** also afforded a single isomer **194b**. The configuration of the adduct **194a** and **194b** was based on the sterically favourable exo approach (Scheme 51) of the Ph and Bu groups from the less hindered face (i.e. α face) of the nitrone.[97] Such a high selectivity is surprising since the C(4)-CMe_2OH group, imparting the facial difference, is positioned at the furthest point from the nitrone functionality in **192**, yet a surprisingly high selectivity in the addition reactions were observed.

The addition of disubstituted alkenes methyl methacrylate (**195**) to the nitrone **192** also demonstrated a very high face- and stereoselectivity (Scheme 51); a nonseparable mixture of adducts **196** and **197** in a respective ratio of 95:5 was obtained. The major adduct **196** was obtained via α-exo (Me) approach. The stereochemistry is based on the precedent lietrature [2a], the parent nitrone 3,4,5,6-tetrahydropyridine 1-oxide is known to

give major and minor adducts in a ratio of 96:4 as a result of a favourable secondary orbital interaction via an endo-oriented methoxycarbonyl group in the transition state.



Scheme 51.

Since the stereochemistry of the ring fusion dictates the regiochemical outcome of the peracid oxidation process leading to the second-generation nitrones (*vide supra*) (Scheme 50), we have examined the conformational aspects as well as composition of the

nitrogen invertomers (if any) by NMR spectroscopy. The presence of −N−O− moiety in an organic molecule has a distinctive place in conformational analysis; [13-15] oxygen being next to nitrogen raises the barrier to nitrogen inversion to such an extent that the individual invertomers can be identified by NMR spectroscopy.[83] At ambient temperature, the ^{1}H and ^{13}C NMR spectra of these cycloadducts show sharp signals indicating the presence of a single invertomer for each of the compounds **194a**, **194b** and **196** as well as their corresponding acetate derivatives **198-200** obtained by reacting the former compounds with acetic anhydride in the presence of 4-(N,N-dimethylamino)pyridine (DMAP) (Scheme 52).

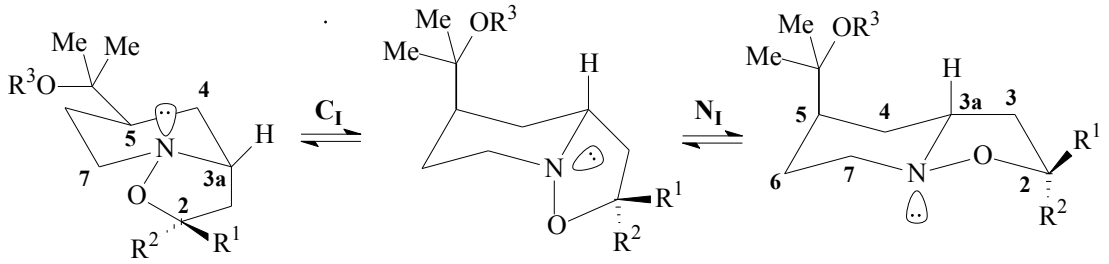
With respect to the six-membered ring, both *cis*-fused **B** and *trans*-fused **C** have the bulky $CMe_2OH(Ac)$ substituent axially-oriented, while the tertiary group is equatorially oriented in *cis*-fused **A**. As such the major cycloadducts **194a**, **194b** and **196a**, as well as their acetates **198-200**, are expected to remain exclusively in the invertomeric form of *cis*-fused **A**. Note that for compound **184a**, the parent 6/5 fused bicyclic isoxazolidine, a *cis/trans* ratio of 22:78 translates into a ΔG^{o} value (determined at -50 °C) of 2.11 kJ mol^{-1} favoring the **184a**-*trans*-fused invertomer, while for a *cis/trans* ratio of 24:76 for cycloadduct **184b**, ΔG^{o} value (determined at +25 °C) becomes 3.13 kJ mol^{-1} (Scheme 50). ^{t}Butyl group is well known to have a conformational enthalpy (ΔH^{o}) difference of 21 kJ mol^{-1}. Comparing cis-fused **A** of **194a** with its trans-fused C, the bulky tertiary substituent CMe_2OH (akin to a ^{t}butyl group) at C(5) is expected to destabilize the latter invertomer by an approximate ΔHo of 21 kJ mol-1, thereby implying an overall free energy (ΔG^{o}) advantage of about 18 kJ mol^{-1} (i.e. 21-3.13) for the *cis*-invertomer. (Note that the entropy difference (ΔS^{o}) between the two invertomeric forms is assumed to be

zero since both the invertomers remain as dl-pairs and have no axis of rotation). Such an astronomical energy difference would predict the complete absence of the *trans* invertomer as far as NMR detection limit is concerned. That the stable invertomers have the configuration of cis-fused **A** as depicted in (Scheme 52) get further credence from ^{1}H NMR spectroscopy. While the C(3a)H is equatorially oriented in *cis*-fused **A**, it is axially oriented in *trans*-fused **C**. The equatorially and axially oriented protons are known[97] to appear at the chemical shift values of δ 3.8 and 3.3 ppm, respectively; the observed chemical shifts of ~δ 3.8 for the current compounds thereby ascertain the equatorial orientation of the C(3a)H in the exclusive invertomer *cis*-fused **A**.

Assertion of the cis fusion of the ring juncture predicts that the synthesis of the desired second-generation aldonitrones regiospecifically may be achieved by the peracid oxidation process mentioned earlier. To our relief and delight, the isoxazolidines **198-200**, on treatment with m-chloroperbenzoic acid (MCPBA) gave the aldonitrones **201-203** exclusively and in almost quantitative yields (Scheme 52). This is the first time a series of 6/5-fused isoxazolidines have been shown to generate the synthetically important aldonitrones regiospecifically.

The peracid oxidation was also carried out in protic solvent ethanol in the hope that it will be able to intercept the intermediate **B** to obtain its protonated species **C** which would then generate both the aldo- and ketonitrones by general base catalysed abstraction of the proton H_a or H_b and H_c, respectively (Scheme 53). The oxidation of **200** with MCPBA in methanol did indeed generate two nitrones **203** and **204** in a respective ratio of 80:20. While the general base catalyzed proton abstraction would favour the formation of more substituted ketonitrone **204**, its formation as a minor isomer certifies a certain degree

of concertedness as depicted in intermediate **A** as well as a competitive abstraction of proton H_b by RO^- in **B** versus the protonation leading to **C**. The nitrones are readily identified by the ^1H NMR spectral analysis. The nonoverlapping H_c, H_d and H_f of aldonitrone **203** appeared at δ4.21, 2.64 (1H, dd, J 10.2, 14.3 Hz), and 7.08, respectively, while for the ketonitrone **204**, the H_g and H_h was displayed at δ 3.90, and H_i and H_j at 3.23 (d, J 13.6 Hz) and 2.74 (d, J 13.6 Hz) ppm.

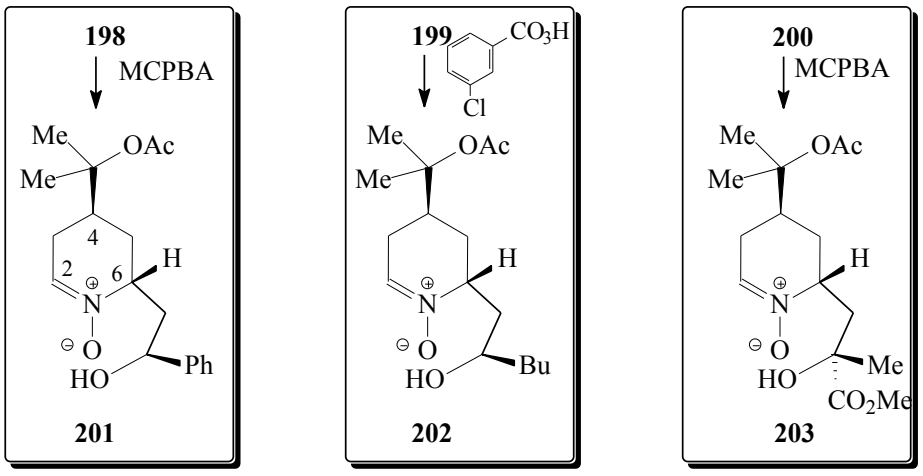


A (*cis*-fused) **Exclusive** **B** (*cis*-fused) **C** (*trans*-fused)

194a, R^1 = Ph; R^2 = R^3 = H
194b, R^1 = Bu; R^2 = R^3 = H
196, R^1 = Me; R^2 = CO_2Me; R^3 = H

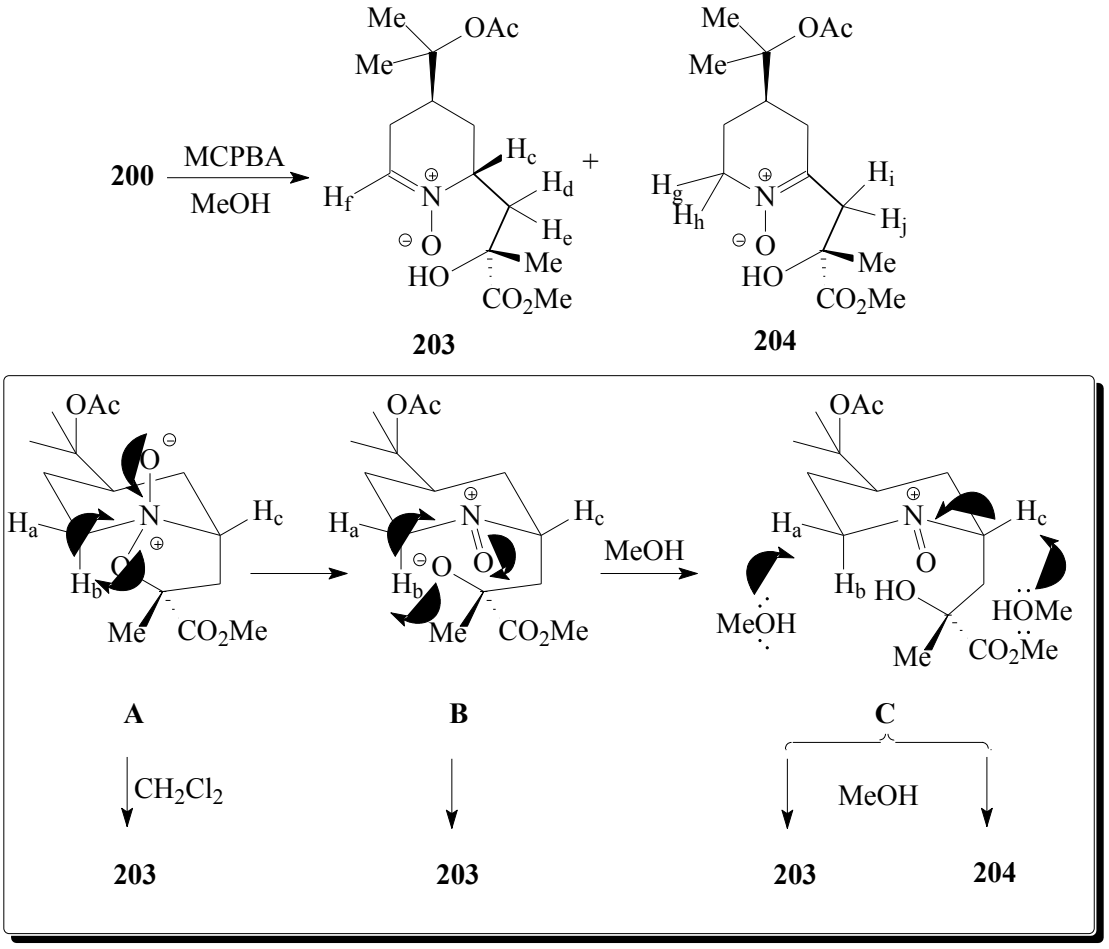
Ac_2O, NMe_2, N

198, R^1 = Ph; R^2 = H; R^3 = Ac
199, R^1 = Bu; R^2 = H; R^3 = Ac
200, R^1 = Me; R^2 = CO_2Me; R^3 = Ac



Scheme 52.

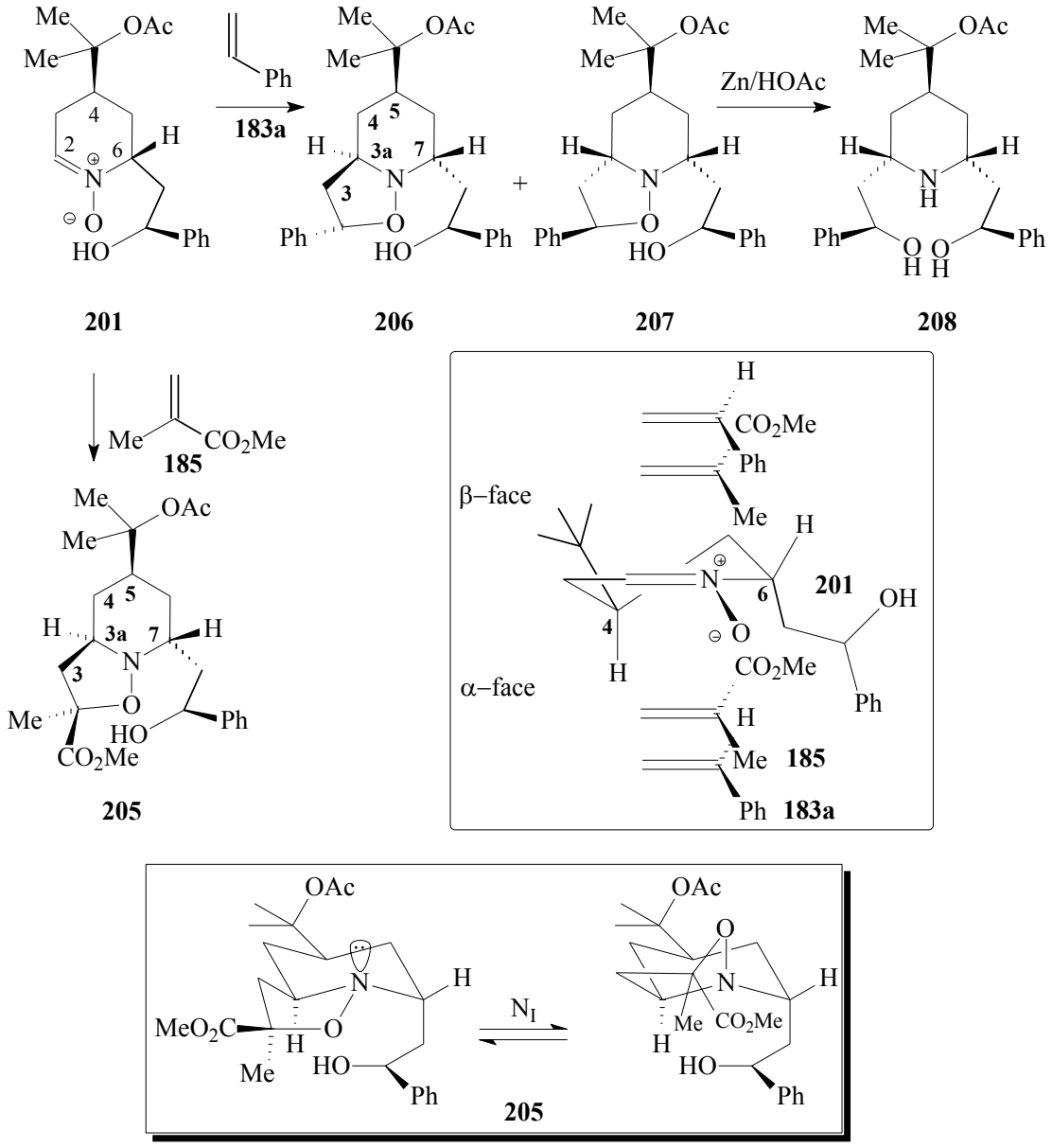
Next, we explored the cycloaddition reaction of the second-generation nitrone **201** with the alkene **183**; a nonseparable mixture of three adducts in a respective ratio of 89:8:~1) was obtained in 91% yield (Scheme 53). The addition was thus found to be highly face selective. The stereochemistry of the major adduct was based on the approach of the alkene from the β-face of the nitrone to give C(3a),C(7)-trans substituted adduct **205**; in the α-face approach, the CO_2Me group is expected to experience severe steric crowding in the transition state. The face selectivity is thus dictated by the steric influence of the substituent at C(6) so as to force the alkene to approach from the β-face of the nitrone wherby the smaller Hs at the unsubstituted end of the alkene are in a better position to negotiate with the steric encumbrance of C(4) substituent. The adduct **205** is expected to be equilibrating between the two invertomers in both of which the bulky tertiary substituent is placed at equatorial orientation. The ^{1}H as well as ^{13}C NMR spectra at ambient temperatures did indeed reveal broad signals.



Scheme 53.

For the addition reaction of styrene **183a** with nitrone **201**, a mixture of isomers **206** and **207** was obtained in a respective ratio of 1:3; the face selectivity is thus dictated by the steric influence of the β–substituent at C(4) so as to force the alkene to a preferable approach from the α-face of the nitrone. The endo-oriented H of styrene will have very little discomfort in compare to the endo-oriented carbomethoxy as far as the steric encumbrance of the α–oriented substituent at C(6) is concerned. The stereochemical analyses thus revealed that the mono- **183a** and disubstituetd **185** alkenes prefer to

approach the α- and β-face of the nitrone, respectively, and the experimental findings are rationalized in terms of the transition state structures depicted in (Scheme 54).



Scheme 54.

The stereochemistry of the addition reaction was confirmed by chemical conversion of **207** into the ring opened product **208** by cleaving the N-O bond of the cycloadducts with zinc/acetic acid. The NMR spectra of the amine **208** ($C_{26}H_{35}NO_4$),

obtained from adduct **207**, confirmed its symmetric nature; as expected the ^{13}C NMR spectrum revealed the presence of 13 carbon signals. The two benzylic protons appeared identical as displayed by a single signal at δ4.96-4.94 (2H, m); even the two phenyl rings appeared identical as displayed by three types of proton at δ7.14 (4H, d, J 7.3 Hz), 7.24 (4H, t, J 7.3 Hz), 7.14 (2H, t, J 7.3 Hz).

The study has confirmed the mechanism of the peracid induced ring opening of the isoxazolidine, and led to the synthetically important second-generation cyclic aldonitrones, for the first time, with a complete regioselectivity. The bulkier tertiary substituent at C(5) in the cycloadducts has, to our advantage, frozen the invertomer exclusively in the *cis*-fused form and thus led to the observed regioselectivity.

5.3 Experimental

5.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTI.R spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at +25°C using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). 4-methoxycarbonylpiperidine (**187**), 1-hexene, styrene, methyl methacrylate, m-chloroperbenzoic acid, from Fluka Chemie AG (Buchs, Switzerland) were used as

received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N_2.

5.3.2. *N*-Benzyl-4-methoxycarbonylpiperidine (188)

To a stirring solution of amine **187** (10 g, 70 mmol) in THF (50 mL) in the presence of triethyl amine (7 g) at 0°C was added benzyl bromide (13.2 g, 70 mmol) dropwise. After stirring at room temperature overnight, the mixture was taken up in water (20 mL) and extracted with CH_2Cl_2 (4×30 mL). The combined organic layers were dried (Na_2SO_4), concentrated and the residual liquid was distilled to give amine **188** as a colorless liquid (15.3 g, 94%), $bp_{0.1\ mbarHg}$ 104 °C; (Found: C, 71.9; H, 8.2; N, 5.8. $C_{14}H_{19}NO_2$ requires C, 72.07; H, 8.21; N, 6.00%.); ν_{max} (neat) 3027, 2949, 2802, 2760, 1732, 1494, 1450, 1435, 1367, 1320, 1286, 1268, 1196, 1167, 1145, 1047, 1014, 983, 906, 738, and 699 cm^{-1}. δ_H 7.21-7.32 (5H, m), 3.67 (3H, s), 3.48 (2H, s), 2.85 (2H, apparent d, *J* 11.9 Hz), 2.29 (1H, tt, *J* 4.0, 11.0 Hz), 2.02 (2H, dt, *J* 2.3, 11.6 Hz), 1.89-1.84 (2H, m), 1.82 -1.71 (2H, m); δ_C 175.7, 138.3, 129.1 (2C), 128.1 (2C), 126.9, 63.2, 52.8 (2C), 51.5, 41.0, 28.2 (2C).

5.3.3. *N*-Benzyl-4-(2-hydroxy-2propyl)piperidine (189)

To a stirring solution of amine **188** (10 g, 42 mmol) in THF (50 mL) at 0 °C was added dropwise a 3M solution of methyl magnesium bromide (30 mL, 90 mmol). The mixture was then stirred at room temperature for 6 h. After addition of a saturated solution of ammonium chloride (20 mL), the aqueous layer was extracted with CH_2Cl_2 (4×30 mL). The combined organic layers was dried (Na_2SO_4), concentrated and the residual liquid was

purified by chromatography over silica using 1:1 ether/methanol mixture as eluant to give the aminoalcohol **189** as a white solid (7.3 g, 75%). Mp 75-76°C (ether-pentane); (Found: C, 77.0; H, 10.1; N, 5.9. $C_{15}H_{23}NO$ requires C, 77.21; H, 9.93; N, 6.00 %.); ν_{max} (KBr) 3366, 2961, 2939, 2861, 2802, 2760, 1452, 1368, 1342, 1269, 1218, 1137, 1090, 997, 920, 759, 739, and 700 cm^{-1}. δ_H 7.32 -7.23 (5H, m), 3.49 (2H, s), 2.97 (2H, apparent d, *J* 11.6 Hz), 1.92 (2H, dt, *J* 2.3, 11.7 Hz), 1.72 -1.66 (2H, m), 1.39 (2H, dq, *J* 3.6, 12.5 Hz), 1.32-1.24 (2H, m), 1.17 (6H, s) ; δ_C 138.0, 129.3 (2C), 128.1 (2C), 127.0, 72.4, 63.2, 54.0 (2C), 47.3, 26.9 (2C), 26.7 (2C).

5.3.4. 4-(2-hydroxy-2propyl)piperidine (190)

The protected aminoalcohol **189** (10 g, 42 mmol) in ethanol (50 mL) containing Pd/C (1 g) was hydrogenated at 20 °C under 50 psi pressure for 3 h. The reaction mixture was filtered over celite and washed with ethanol (2×10 mL). After removal of the solvent, the residue was crystallized from acetone to give the pure aminoalcohol **190** as a white solid (4.3 g, 72%); mp 136-137°C (Lit.[98] mp 135-137°C); ν_{max} (KBr) 3387, 2970, 2856, 1643, 1632, 1537, 1470, 1426, 1380, 1307, 1276, 1254, 1172, 1117, 915 and 818 cm^{-1}. δ_H 3.23 (2H, apparent d, *J* 12.2 Hz), 2.92 (2H, br s), 2.63 (2H, t, *J* 11.7 Hz), 1.79 (2H, apparent d, *J* 12.6 Hz), 1.46-1.28 (3H, m), 1.18 (6H, s); δ_C 72.4, 47.6, 46.8 (2C), 27.7 (2C), 26.7(2C).

5.3.5. 4-(2-hydroxy-2propyl)-N-hydroxypiperidine (191)

To a stirring solution of aminoalcohol **190** (10 g, 70 mmol) in water (100 mL) in the presence of sodium tungstate (0.8 g) at 0°C under N_2 was added dropwise a 30% H_2O_2

solution (18.5 g, 163 mmol) in 15 min. The mixture was then stirred at 20°C for 2 h. Solid sodium borohydride (2 g, 54 mmol) was added in portions to the above mixture and stirring continued for 1 h. The mixture was extracted with CH_2Cl_2 (4×50 mL). The combined organic layers was dried (Na_2SO_4), concentrated and the residual liquid was purified by chromatography over silica using 70:30 ether/methanol mixture as eluant to give the hydroxylamine **191** as a colorless liquid (8 g, 71%). (Found: C, 60.2; H, 10.6; N, 8.7. $C_8H_{17}NO_2$ requires C, 60.35; H, 10.76; N, 8.80%.); ν_{max} (neat) 3349, 2966, 2861, 2830, 1659, 1449, 1377, 1301, 1254, 1162, 1131, 1099, 1049, 921, 794, 733 cm^{-1}. δ_H 3.37-3.28 (2H, m), 2.47 (2H, t, *J* 10.5 Hz), 1.85-1.75 (2H, m), 1.50-1.37 (4H, m), 1.35-1.27 (1H, m), 1.17 (6H, s) ; δ_C 72.03, 58.66 (2C), 45.93, 27.13 (2C), 26.53 (2C).

5.3.6. 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide (192)

To a solution of the hydroxylamine **191** (4.5 g, 28.2 mmol) in EtOH (50 mL) was added yellow HgO (12.0 g, 56.4 mmol) and the mixture was stirred at 20°C for 6 h or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and $MgSO_4$. The bed was washed with liberal excess of ethanol. The formation of the nitrone was assumed quantitative for the percent yield calculation in the subsequent cycloaddition reactions. However, the nitrone contained minor quantities of impurities and as such its elemental analysis was not carried out. ν_{max} (neat) 3360, 2972, 2938, 1633, 1446, 1369, 1299, 1245, 1162, 1047, 950, 924, 790, 732 and 478 cm^{-1}. δ_H 7.18-7.15 (1H, m), 3.90-3.81 (2H, m), 2.55-2.48 (1H, m), 2.43-2.28 (2H, m), 2.13-2.10 (1H, m), 1.70-1.83 (2H, m), 1.25 (3H, s), 1.24 (3H, s); δ_C 137.0, 70.8, 58.2,

40.1, 27.3 (Me), 27.1, 26.9 (Me), 23.9. Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

5.3.7. 2-Phenyl-5-(2-hydroxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (194a)

A solution of nitrone **192** (10 mmol) in EtOH (40 mL) containing styrene **(193a)** (5 mL) was heated at 90°C for 4 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was purified by chromatography over silica using 85:15 ether/methanol as eluant to give a single adduct **194a** as a white solid (2.0 g, 80%). ^1H NMR of the crude or the separated fraction failed to reveal the presence of any other minor isomers. *m/z* 261 [M^+]; Mp 87-89°C (ether-pentane); (Found: C, 73.3; H, 8.7; N, 5.3. $C_{16}H_{23}NO_2$ requires C, 73.53; H, 8.87; N, 5.36%.); ν_{max} (neat) 3358, 2968, 2927, 2865, 1494, 1452, 1380, 1367, 1293, 1264, 1206, 1170, 1152, 1119, 1093, 952, 921, 758, 731, and 700 cm^{-1}; δ_H 7.40-7.25 (5H, m), 5.40 (1H, dd, *J* 3.8, 9.9 Hz), 3.92-3.85 (1H, m), 3.25 (1H, td, *J* 3.4, 10.4 Hz), 2.83 (1H, ddd, J 2.5, 10.4, 12.8 Hz), 2.75 (1H, dt, *J* 10.0, 12.0 Hz), 2.05-1.70 (5H, m), 1.62-1.54 (1H, tt, *J* 3.0, 12.0 Hz), 1.52-1.42 (1H, dq, *J* 3.4, 12.8 Hz), 1.21 (3H, s), 1.20 (3H, s); δ_C 142.3, 128.4 (2C), 127.6, 126.4 (2C), 78.8 (C-Ph), 72.1 ($\underline{C}Me_2$), 60.2, 49.9, 40.8 ($\underline{C}CMe_2$), 38.8, 27.1 (Me), 27.0 (Me), 26.2, 25.8. Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

5.3.8. 2-Butyl-5-(2-hydroxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (194b)

A solution of nitrone **192** (10 mmol) in EtOH (40 mL) containing 1-hexene **(193b)** (10 mL) was heated at 90°C for 20 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was purified by chromatography over

silica using 95:5 Dichloromethane/methanol as eluant to give only one adduct **194b** as a colorless liquid (1.85 g, 75%). *m/z* 241 [M^+]; mp 87-89°C (ether-pentane); (Found: C, 69.4; H, 11.1; N, 5.7. $C_{14}H_{27}NO_2$ requires C, 69.67; H, 11.27; N, 5.80%.); ν_{max} (neat) 3397, 2958, 2929, 2872, 1666, 1454, 1379, 1369, 1291, 1265, 1210, 1140, 1098, 954, 926, and 761 cm^{-1}; δ_H 4.42-4.36 (1H, m), 3.64-3.58 (1H, m), 3.11 (1H, td, *J* 3.4, 10.4 Hz), 2.68 (1H, ddd, *J* 2.5, 10.2, 12.8 Hz), 2.36 (1H, dt, *J* 9.4, 11.9 Hz), 1.97-1.20 (13H, m), 1.19 (3H, s), 1.18 (3H, s), 0.90 (3H, t, *J* 7 Hz); δ_C 77.2, 72.1, 59.7, 49.6, 40.7, 35.35, 35.26, 28.1, 27.0 (2C), 26.3, 25.7, 22.7, 14.0.

5.3.9. Isomers of Methyl 2-methyl-5-(2-hydroxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine-2-carboxylate (196 and 197)

A solution of nitrone **192** (10 mmol) in EtOH (40 mL) containing methyl methacrylate **(195)** (6 mL) was heated at 50°C for 3 h under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture was separated by chromatography over silica using 95: 5 DCM/methanol as eluant to give a nonseparable mixture of adducts **196** and **197** in a respective ratio of 95:5 as a colorless liquid (2.1 g, 83%). The presence of the minor adduct was revealed by the presence of a CO_2Me singlet at 3.75 ppm. Mp 128-129°C (ether-pentane); (Found: C, 60.5; H, 9.1; N, 5.3. $C_{13}H_{23}NO_4$ requires C, 60.68; H, 9.01; N, 5.44%.); ν_{max} (neat) 3404, 2968, 2930, 2872, 1731, 1652, 1454, 1371, 1293, 1251, 1217, 1191, 1139, 1114, 1084, 987, 946, 920, 874, 738 and 667 cm^{-1}; δ_H 3.77 (3H, s), 3.79-3.74 (1H, m), 3.18 (1H, td, *J* 3.4,10.4 Hz), 2.90 (1H, t, *J* 12.5 Hz), 2.65 (1H, ddd, *J* 2.5, 10.7, 13.0), 2.00-1.93 (2H, m), 1.91-1.33 (1H, m), 1.79-1.71 (2H, m), 1.54 (1H, tt, *J* 3.0, 12.8 Hz), 1.50 (3H, s), 1.43-1.33 (1H, dq, J 3.4, 12.8 Hz),

1.19 (3H, s), 1.18 (3H, s); δ_C 175.6, 84.2, 72.0, 60.3 (CHN), 52.6 (CO_2Me), 50.8, 40.8 ($CHCMe_2$), 39.6, 27.0 (2C, CMe_2), 25.86 (2C), 25.75 (C-Me). Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

5.3.10. 2-Phenyl-5-(2-acetoxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (198)

The cycloadduct **194a** (1.10 g, 4.3 mmol) in toluene (20 mL) was treated with acetic anhydride (3 mL) and DMAP [4-(*N,N*-dimethylamino)pyridine] (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride, the residual liquid was purified by chromatography over silica gel using 1:1 ether/hexane as eluant to give the acetate **18** as a white solid (1.24 g, 95%). Mp 58-60°C (ether-pentane); (Found: C, 71.0; H, 8.1; N, 4.7. $C_{18}H_{25}NO_3$ requires C, 71.26; H, 8.31; N, 4.62%.); ν_{max} (KBr) 2977, 2951, 2930, 2857, 1728, 1494, 1453, 1368, 1257, 1150, 1133, 1018, 949, 758, and 701 cm^{-1}; δ_H 7.37-7.25 (5H, m), 5.40 (1H, dd, *J* 3.8, 9.9 Hz), 3.93-3.80 (1H, m), 3.27 (1H, td, *J* 3.4,10.3 Hz), 2.84 (1H, ddd, *J* 2.7, 10.3, 12.8 Hz), 2.76 (1H, dt, *J* 10.1, 12.0 Hz), 2.23 (1H, tt, *J* 3.35, 12.3 Hz), 2.04 (1H, ddd, *J* 3.4, 7.6, 12.3 Hz), 1.98 (3H, s), 1.98-1.91 (1H, m), 1.88-1.91 (1H, m), 1.77-1.71 (1H, m), 1.52 (1H, dq, *J* 3.1, 12.8 Hz), 1.45 (3H, s), 1.43 (3H, s); δ_C 170.5, 142.2, 128.5 (2C), 127.6, 126.4 (2C), 84.0 (CPh), 78.9 (CMe_2CO), 60.0, 49.8, 38.8, 38.2 ($CCMe_2$), 25.8, 25.5, 23.47 (CMe), 23.44 (CMe), 22.4 $COCH_3$).

5.3.11. 2-Butyl-5-(2-acetoxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a]pyridine (199)

The cycloadduct **194b** (1.30 g, 5.4 mmol) in toluene (10 mL) was treated with acetic anhydride (3 mL) and DMAP [4-(N,N-dimethylamino) pyridine] (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride the

residual liquid was purified by chromatography over silica gel using 80:20 ether-Hexanes as eluant to give the acetate **199** as a colourless liquid (1.30 g, 85%). *m/z* 283 [M^+]; (Found: C, 67.6; H, 10.2; N, 4.8. $C_{16}H_{29}NO_3$ requires C, 67.81; H, 10.31; N, 4.94%.); ν_{max} (neat) 2955, 2930, 2858, 1729, 1454, 1431, 1368, 1256, 1222, 1153, 1134, 1018, 946, and 759 cm^{-1}; δ_H 4.43-4.36 (1H, m), 3.67-3.58 (1H, m), 3.11 (1H, td, *J* 3.4,10.40 Hz), 2.68 (1H, ddd, *J* 2.7, 10.4, 12.9 Hz), 2.36 (1H, dt, *J* 9.4, 11.9 Hz), 2.16 (1H, tt, *J* 4.0, 11.9 Hz), 1.97 (3H, s), 1.90-1.76 (2H, m), 1.73-1.55 (4H, m), 1.53-1.25 (5H, m), 1.43 (3H, s), 1.41 (3H, s), 0.90 (3H, t, *J* 7.0 Hz); δ_C 170.5, 84.1, 77.3, 59.7, 49.6, 38.2, 35.34, 35.29, 28.2, 26.0, 25.5, 23.48, 23.42, 22.7, 22.4, 14.0.

5.3.12. Methyl-2-methyl-5-(2-acetoxy-2-propyl)hexahydro-2H-isoxazolo[2,3-a] pyridine-2-carboxylate (200)

The cycloadduct **196** (1.90 g, 7.4 mmol) in toluene (10 mL) was treated with acetic anhydride (3 mL) and DMAP (0.12 g, 1 mmol) at 70 ºC for overnight. After removal of the solvent and excess acetic anhydride the residual liquid was purified by chromatography over silica gel using 80:20 ether-hexanes as a eluant to give the acetate 200 as a colourless liquid (1.99 g, 90%). (Found: C, 60.0; H, 8.3; N, 4.6. $C_{15}H_{25}NO_5$ requires C, 60.18; H, 8.42; N, 4.68%.); ν_{max} (neat) 2959, 2951, 1730, 1454, 1370, 1255, 1192, 1137, 1116, 1086, 1019, 988, 947, 873, 757, and 608 cm^{-1}. δ_H 3.78 (3H, s), 3.80-3.75 (1H, m), 3.18 (1H, td, *J* 3.4,10.4 Hz), 2.87 (1H, t, *J* 12.5 Hz), 2.66 (1H, ddd, *J* 2.5, 10.7, 13.0), 2.11-2.02 (1H, m), 1.96 (3H, s), 1.70-1.63 (1H, m), 1.99-1.82 (3H, m), 1.50 (3H, s), 1.43 (3H, s), 1.41 (3H, s), 1.45-1.36 (1H, m); δ_C 175.5, 170.4, 84.3, 83.8, 60.1 (<u>C</u>HN), 52.7(O<u>Me</u>),

50.6, 39.5, 38.7 ($\underline{C}HCMe_2$), 25.8 (Me), 25.6, 25.4, 23.4 (Me), 23.3 (Me), 22.4 (Me). Assignment of the ^{13}C chemical shifts was based on DEPT experiment results.

5.3.13. 4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-2-phenyl-1-ethyl)-3,4,5,6-tetrahydropyridine 1-oxide (201)

To a stirred solution of the cycloadduct **198** (3.0 mmol) in dichloromethane (30 mL) at 20ºC was added MCPBA (3.0 mmol) in one portion. After 30 min at 20 ºC the organic layer was washed with 5% $NaHCO_3$ solution (3×10 mL). The combined aqueous layers was re-extracted with CH_2Cl_2 (3×25 mL). The combined organic layers was dried (Na_2SO_4), concentrated to give only the aldonitrone **201** as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. ν_{max} (neat) 3250, 2981, 2929, 1729, 1621, 1493, 1454, 1431, 1370, 1257, 1224, 1167, 1138, 1098, 1019, 914, 760, 733, and 703 cm^{-1}; δ_H 7.43-7.21 (5H, m), 7.21-7.17 (1H, m), 6.17 (1H, br s), 5.08-5.03 (1H, dd, *J* 2.7, 6.4 Hz), 4.15-4.08 (1H, m), 2.55-2.45 (1H, m), 2.42-2.30 (3H, m), 2.03-1.98 (1H, m), 1.97 (3H, s), 1.88–1.82 (1H, m), 1.72-1.67 (1H, m), 1.46 (3H, s), 1.42 (3H, s); δ_C 170.1, 143.8, 137.5, 128.3 (2C), 127.0, 125.7 (2C), 82.2, 70,2, 63.1, 44.2, 34.4, 29.9, 27.0, 23.2, 23.1, 22.2.

5.3.14. 4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-1-hexyl)-3,4,5,6-tetrahydropyridine 1-oxide (202)

The cycloadduct **199** (3.0 mmol) was treated with MCPBA to generate the aldonitrone **202** as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. ν_{max} (neat) 3357, 2932,

2871, 1729, 1631, 1454, 1370, 1256, 1224, 1170, 1139, 1019, 921, 788, and 732 cm^{-1}; δ_H 7.16 (1H, t, *J* 3.8 Hz), 5.02 (1H, br s), 4.33-4.22 (1H, m), 3.92-3.78 (1H, m), 2.55-2.30 (4H, m), 2.10-1.90 (2H, m), 2.00 (3H, s), 1.88-1.80 (1H, m), , 1.70-1.22 (6H, m), 1.50 (3H, s), 1.47 (3H, s), 0.91 (3H, t, *J* 7.0 Hz), δ_C 170.2, 136.7, 82.4, 68.2, 63.7, 42.1, 36.5, 34.2, 29.2, 28.2, 26.9, 23.3, 23.2, 22.7, 22.3, 14.1.

5.3.15. 4-(2-Acetoxy-2-propyl)-6-(2-hydroxy-2-carbomethoxy-1-propyl)-3,4,5,6-tetrahydropyridine 1-oxide (203)

The cycloadduct **200** (3.0 mmol) was treated with MCPBA to generate the aldonitrone **203** as a pale yellow liquid in almost quantitative yield. The crude nitrone was not purified further and its elemental analysis was not carried out. ν_{max} (neat) 3438, 2981 1728, 1713, 1644, 1631, 1554, 1537, 1516, 1452, 1371, 1256, 1137, 1020, 918, 732, 645 and 611 cm^{-1}. δ_H 7.09-7.06 (1H, m), 6.46 (1H, br s), 4.24-4.18 (1H, m), 3.75 (3H, s), 2.64 (1H, dd, J 10.2, 14.3 Hz), 2.58-2.25 (3H, m), 1.99 (3H, s), 2.02-1.77 (2H, m), 1.51 (3H, s), 1.50 (3H, s), 1.48 (3H, s), 1.54-1.37 (1H, m); δ_C 176.2, 170.0, 137.5, 82.1, 73.2, 62.4, 52.4, 43.6, 34.7, 28.9, 26.8, 26.7, 23.2 (2C), 22.2.

5.3.16. Reaction of nitrone 201 with methymethacrylate (185)

The nitrone **201** [prepared by MCPBA oxidation of adduct **198** (1.0 mmol)] in CH_2Cl_2 (10 mL) was treated with methyl methacrylate **(185)** (1.0 mL) and the mixture was stirred at 45ºC for overnight. After removal of the solvent and excess alkene, the residual liquid was purified by chromatography over silica gel using 9:1 ether/hexane as eluant to give a nonseparable mixture of three adducts (as indicated by the presence of three CO_2Me

singlets at δ3.77, 3.80 and 3.84 ppm in a respective ratio of 89:8:~1 as a colourless liquid (380 mg, 91%). The major adduct was assigned the stereochemistry of **205**. (Found: C, 65.6; H, 7.7; N, 3.2. $C_{23}H_{33}NO_6$ requires C, 65.85; H, 7.93; N, 3.34%.); ν_{max} (neat) 3475, 2982, 2951, 2872, 1728, 1653, 1448, 1368, 1254, 1215, 1125, 1057, 1020, 936, 754, 700, 609 cm^{-1}; δ_H 7.40-7.23 (5H, m), 5.00 (1H, m), 3.77 (3H, s), 3.77-3.70 (2H, m), 2.43-2.20 (4H, m), 1.95 (3H, s), 1.98-1.22 (6H, m), 1.56 (3H, s), 1.37 (3H, s), 1.35 (3H, s); δ_C 174.2, 170.3, 144.6, 128.3 (2C),126.9, 125.5 (2C), 84.1, 80.3, 72.6, 56.0, 54.8, 52.6, 46.2, 38.4 (2C), 27.5, 25.4 (2C), 23.14, 23.06, 22.4.

5.3.17. Reaction of nitrone 201 with styrene (193a)

The Nitrone **201** [prepared by MCPBA oxidation of adduct **198 (**2.0 mmol)] in CH_2Cl_2 (10 mL) was treated with styrene (2.0 mL) and the mixture was stirred at 45ºC for overnight. After removal of the solvent and excess alkene, the residual liquid was separated by chromatography over silica gel using 7:1 ether/hexane as eluant to give the minor isomer **206** as a colorless liquid (90 mg). Continued elution gave a mixture of **206** and **207**. Finally, the major adduct **207** was eluted as a colorless liquid. The total isolated yield was 82% and respective ratio of **206** and **207** was found to be 1:3.

5.3.17.1. Minor diastereomer 206.

(Found: C, 77.4; H, 7.7; N, 3.2. $C_{26}H_{33}NO_4$ requires C, 73.73; H, 7.85; N, 3.31%.); ν_{max} (neat) 3446, 3027, 2947, 2880, 1725, 1656, 1493, 1454, 1369, 1258, 1221, 1132, 1055, 1020, 946, 913, 759, 733 and 701 cm^{-1}; δ_H 7.40-7.20 (10H, m), 5.13-5.09 (1H, m), 5.06-5.02 (1H, m), 3..72-3.60 (2H, m), 2.50- 2.28 (5H, m), 1.98 (3H, s), 1.75-1.22

(5H, m), 1.41 (3H, s), 1.38 (3H, s); δ_C 170.4, 144.6, 141.7, 128.5 (2C), 128.2 (2C), 127.4, 126.8, 125.6 (4C), 84.2, 76.5, 72.3, 56.3, 54.4, 44.6, 39.6, 38.4, 27.3, 25.2, 23.1 (2C), 22.4.

5.3.17.2. Major distereomer: 207.

(Found: C, 73.4; H, 7.6; N, 3.2. $C_{26}H_{33}NO_4$ requires C, 73.73; H, 7.85; N, 3.31%.); ν_{max} (neat) 3429, 3064, 3026, 2945, 1726, 1451, 1367, 1253, 1136, 1018, 782, 753, and 698 cm^{-1}; δ_H 7.40-7.20 (10H, m), 5.20-5.05 (2H, m), 4.60 (1H, br s), 3.41-3.32 (1H, m), 3.10-3.00 (1H, m), 2.50-1.40 (9H, m), 1.96 (3H, s), 1.52 (6H, s); δ_C 170.1, 144.7, 141.8, 128.4 (2C), 128.2 (2C), 127.8, 126.9, 126.4 (2C), 125.7 (2C), 84.3, 78.6, 71.5, 61.3, 59.2, 43.9, 43.6, 40.3, 29.7, 29.3, 24.8, 24.2, 22.6.

5.3.18. Conversion of 207 to 208 by treatment with zinc and acetic acid

To a vigorously stirred solution of the adduct **207** (0.3 mmol) in acetic acid (2 mL) and water (2 mL) at 60 °C was added Zn (0.85 g) in two portions (ca. 5 min). The reaction mixture was stirred at 60°C for a total 30 min. The reaction mixture was decanted and the residual solid was washed with water (10 mL) and CH_2Cl_2 (20 mL). After basification (K_2CO_3), the aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The organic layer was dried (Na_2SO_4), concentrated to give the amine **208** in almost quantitative yield. (Found: C, 73.1; H, 8.0; N, 3.2. $C_{26}H_{35}NO_4$ requires C, 73.38; H, 8.29; N, 3.29%.); ν_{max} (neat) 3410, 3297, 2978, 2858, 1737, 1444, 1373, 1254, 1221, 1113, 1058, 938, 754, 704, and 616 cm^{-1}; δ_H (500 MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 7.14 (4H, d, *J* 7.3 Hz), 7.24 (4H, t, *J* 7.3 Hz), 7.14 (2H, t, *J* 7.3 Hz), 4.96-4.94 (2H, m), 3.97 (3H, br, OHs and NH), 3.01-2.97 (2H, m), 2.02-1.38 (12 H, including a broad signal for OAc, m), 1.27(6H, s) ; δ_C (500

MHz, 9:1 $CDCl_3/CD_3OD$, 25 °C) 169.7, 143.0 (2C), 128.4 (4C), 126.9 (2C), 125.4 (4C), 84.3, 70.6 (2C), 49.6 (2C), 41.8 (2C), 40.7, 30.2 (2C), 24.8 (2C), 21.8.

CHAPTER 6

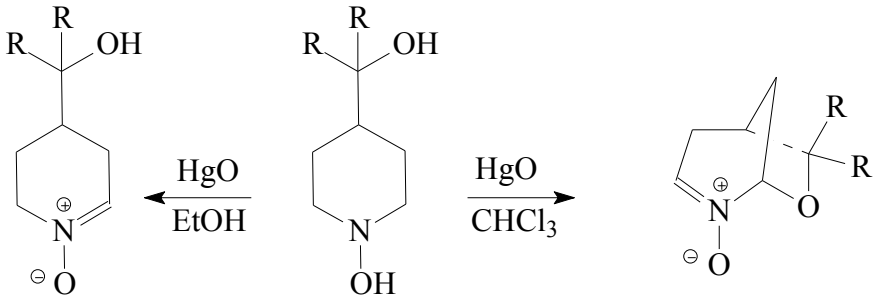
Cycloaddition reaction of a novel class of nitrones: 1-Oxa-6-azabicyclo[3,2,1]-5-heptene 6-oxide

Summary:

One interesting finding was that treatment of the first generation nitrone i.e., 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide or 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide, with mercury(II) oxide afforded novel bicyclic nitrones, 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxides, whose cycloaddition reactions were briefly examined.

6.1 Introduction

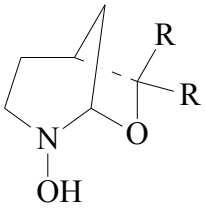
4-hydroxymethyl- and 4-(2-hydroxy-2-propyl)- substituents in the previous cyclic nitrones were our desire to study the effect of these substituents on the *cis: trans* ratio and then there effect on the second generation nitrone upon reacting the adducts with MCPBA. While the mercury(II) oxide oxidation of **139** and **181** in protic solvent ethanol afforded cleanly the monocyclic nitrone **140** and **182** respectivly, the oxidation in aprotic solvent chloroform gave the novel bicyclic nitrone **209** and **210** in almost quantitative yield (Scheme 55).



140: R = H
182: R = Me

139: R = H
181: R = Me

209: R = H
210: R = Me

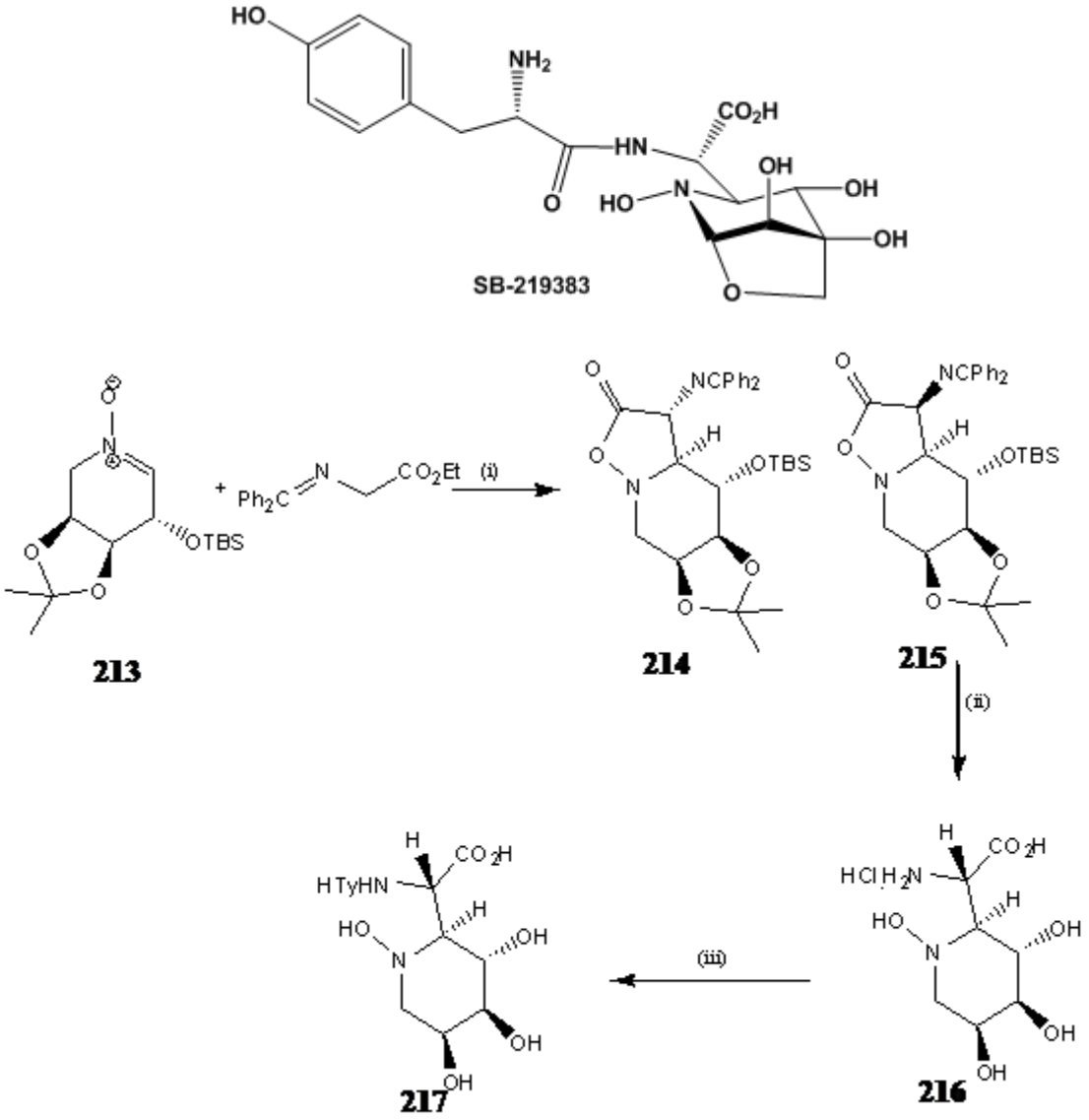


211: R = H
212: R = Me

Scheme 55.

Database searching indicated that this type of nitrones were novel and new. Also substructure search leads us to a novel type of natural product called SB-219383[99] which is a tyrosyl tRNA synthetase inhibitor. SB-219383, isolated from fermentation of broth of a novel species of *Micromonospora sp.,* is the first member of new class of compounds having inhibitory activity against tyrosyl tRNA sythetase (IC_{50} 2 nM). SB-219383 also exhibits moderate in vitro activity against some Gram positive bacteria [100]. The relative stereochemical arrangement within the bicyclic moiety could be deduced from NMR experiments, while the relative stereochemistry between the amino acid α-stereocentre and the ring system as well as the absolute configuration of this C-terminal amino acid remained elusive. Hamprecht *et.al*. [101] synthesized four stereoisomeric analogues, to identify the correct stereostructure of the SB-219383, of SB-219383 (Scheme 53). The four stereoisomers were tested as an inhibitor of bacterial tyrosyl tRNA

syntheatase. One of these isomers was found to be potent inhibitor with an IC_{50} 1.2 nM, while the others are not. The proton NMR data for this potent isomer is almost identical (with the exception of the obvious differences resulting from the omission of the methylenoxy unit of SB-219383).



Scheme 53. (i) LiHMDS, Toluene, -78 oC to rt. (ii) HCl, H_2O, dioxane, 25oC. (iii) $F_3CC(O)NMeTMS$, iPr_2EtN, pyridine, 25oC; BocTyrOSu, 60oC; MeOH, H_2O

The objective of this work is to study the stereo-and face –selectivity of the cycloaddition reaction of this new class of bicyclic nitrones. Then, to study the relationship between the stereochemistry, in the addition reaction of the bicyclic nitrones **209**, **210** and the monocyclic nitrones **140**, **192**. This cycloaddition protocol may have the potential application in the synthesis of piperidine alkaloids in which we can absolutely control the stereochemistry of the cycloaddition. However, this new tricyclic adducts can be considered as a cyclic N, O-acetal, in which the reactivity should be greatly enhanced due to the isoxazolidine ring. This special type of tricyclic adducts might react very easily with electrophiles as well as nucleophiles, so, it could be considered as a masked (or protected) piperidines.

6.2 Results and Discussion

The very idea of having a 4-hydroxymethyl substituent in the current cyclic nitrone was our desire to synthesize a nitrone with an unusual bicyclic system as shown in (Scheme 55) [97]. Surprisingly, mercury(II) oxide oxidation of **139** and **181** in aprotic solvent chloroform gave the novel bicyclic nitrone **209** and **210** in almost quantitative yield. The polar functionality of nitrone **140** and **182** is strongly solvated in ethanol; as a result, the internal aminalization of the nitrone moiety to the N-hydroxy compounds **211** and **212** is discouraged. In an aprotic solvent, further oxidation of the intermediates **21**1 and **212** led to the bicyclic nitrones **209** and **210**.

Next, we pursued the addition reaction of nitrones **209** and **210** with various alkenes. The addition of monosubstituted alkene 1-hexene **141a** and styrene **141b** was found to be stereo-, as well as highly face-selective. A mixture of diasteromers **218a** and **222a** was obtained in a ~19:1 ratio. The configuration of the major adduct **218a** was based on the

sterically favourable exo approach (Scheme 57) of the Bu group from the less hindered face (i.e. β face) of the nitrone, while the α–exo approach of the alkene afforded the adduct **222a**. In order to confirm the stereochemistry of the cycloadducts, the compounds **218a,b** which are the major adducts were converted into **144a,b** in which the latter compounds have a known configuration (Scheme 58). It was surprising that the face selectivity is reversed. This is attriputed to the big difference between the two faces of the bicyclic nitrones, in which the α-face contains seven membered ring while the β-face has a six membered ring. Next we did another cycloaddition reaction with a disubstituted alkene (methylmethacrylate **153**), at this stage we could not purify the adducts but the crude ^{1}HNMR showed two adducts. Then we decided to reduce the crude adducts with $LiAlH_4$, hoping that we can purify the reduced products. This has been done according to (Scheme 58), we were able to seperate two products in wchich we got the same results, that the major adduct was in agreement with the minor adduct from the previous work [97].

Next, nitrone **209** was reacted with methyl acrylate to study the face and stereoselectivity. It was surprising that the additon was α-exo(due the secondery orbital interaction it should be α-endo). This means that the nitrone **209** can not accommodate any substituent to endo due to a steric effect. The cycloaddition also gave another regioisomer i.e 4-substitiuted isoxazolidine. To confirm the sructure for the 5-isome of the mathyl acrylate adduct x-ray crystal strucure (Figure 9.) showed that the orientaion of the CO2Me is exo and at C-5 of the isoxazolidine ring. Also, the piperidine ring is in the distorted chair conformation due the strain. One important properties of these cycloadducts is the very sharp signal in ^{1}H-nmr which means the absence of any nitrogen process. This is due the strian in the tricyclic compounds i.e the strain prevents any inversion.

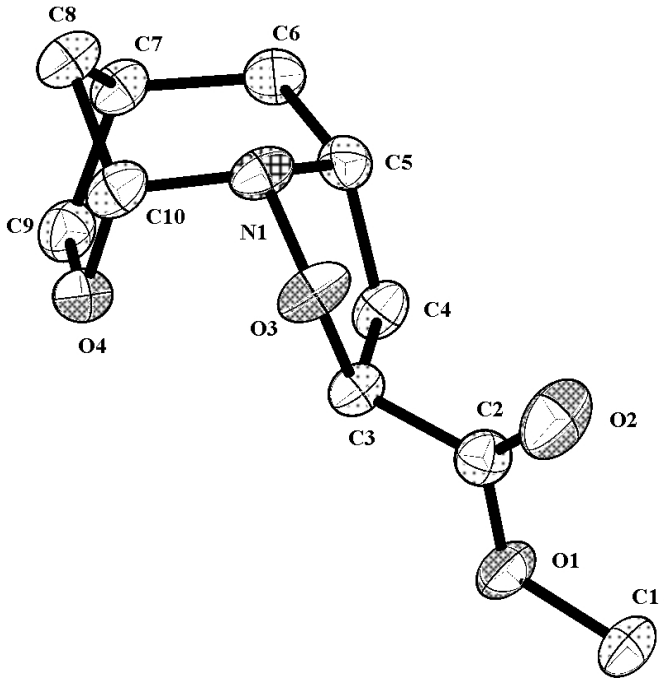
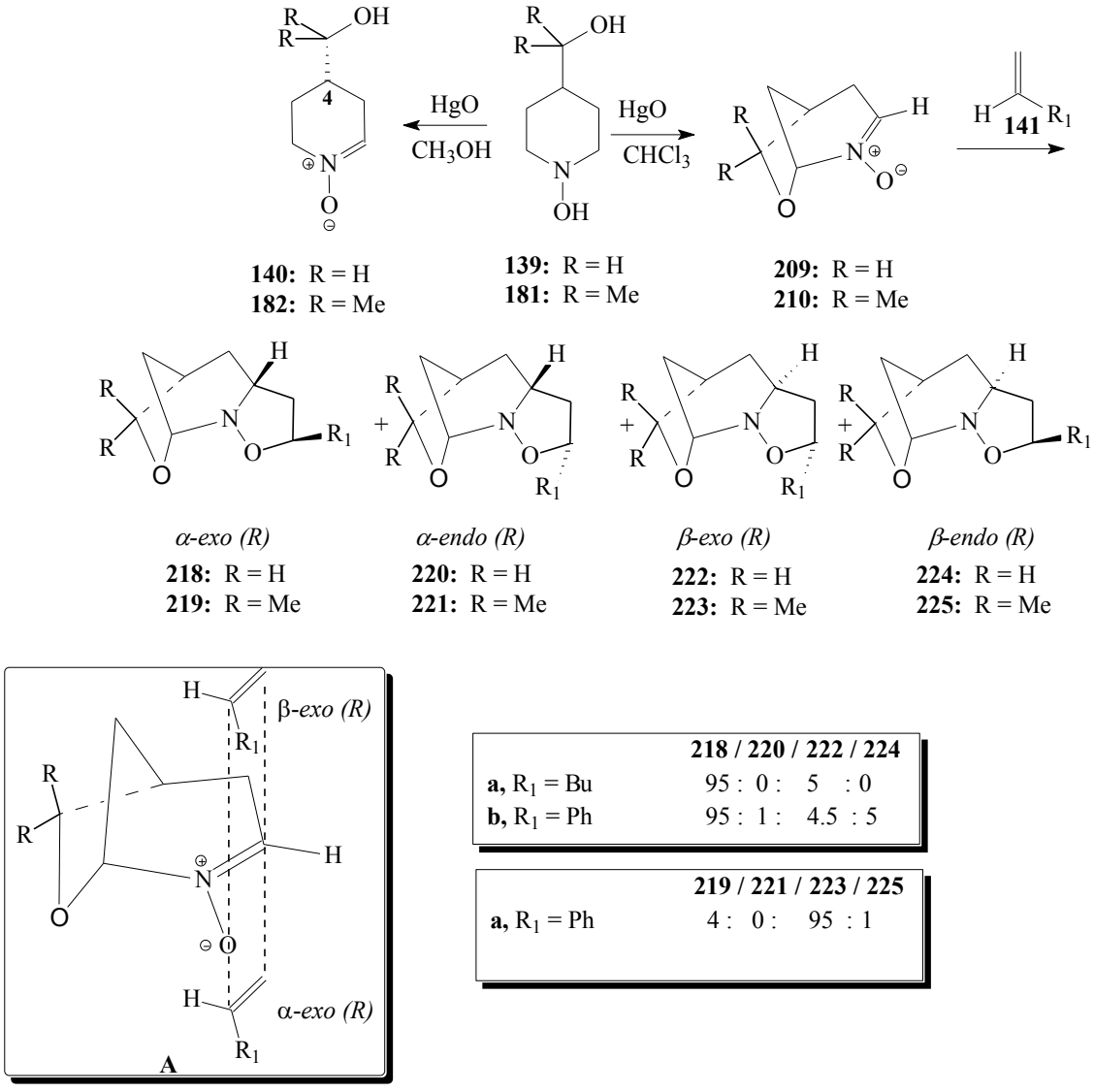


Figure 9. Molecular structure of compound **218c**.

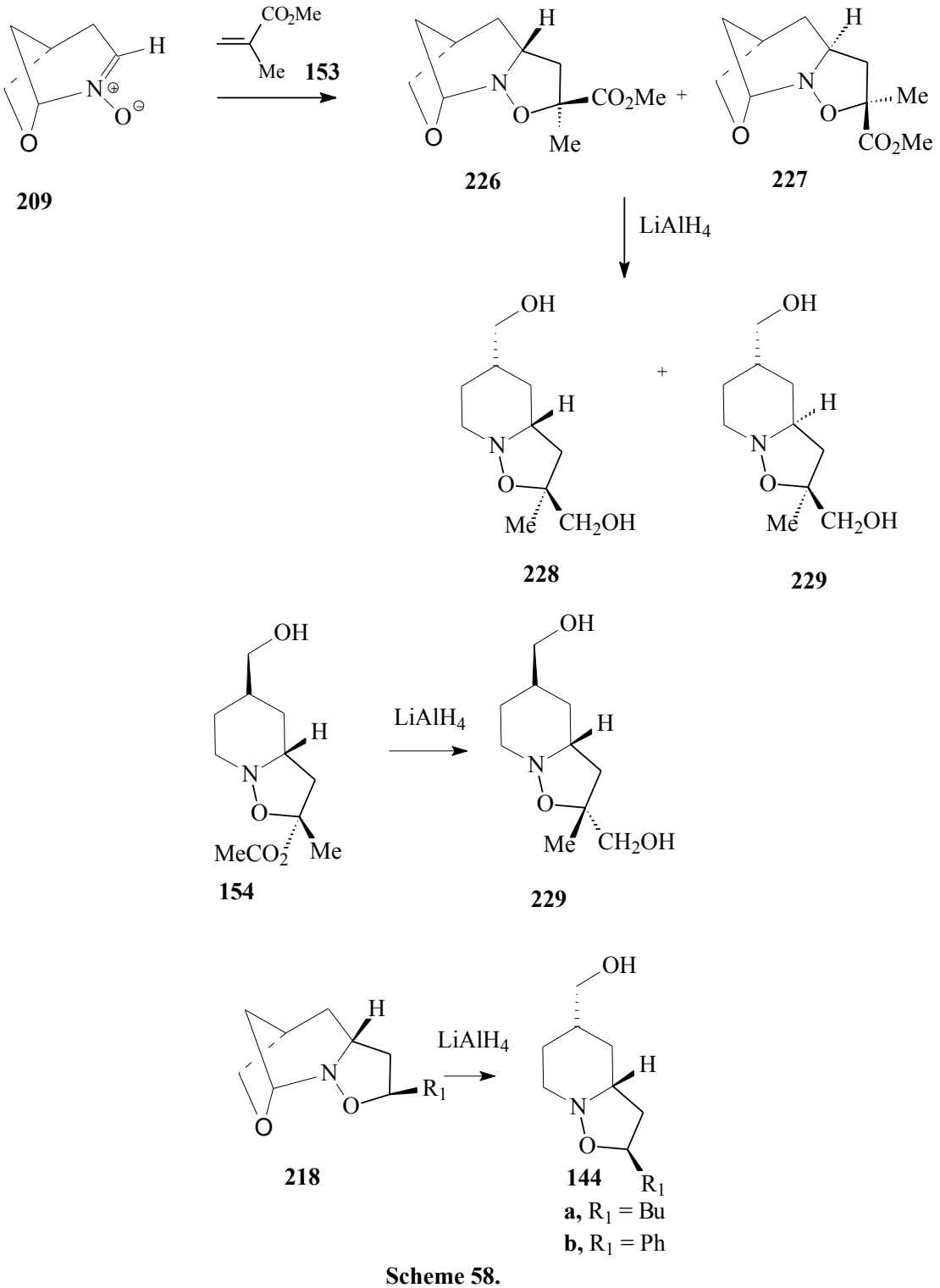


	218 / 220 / 222 / 224
a, R_1 = Bu	95 : 0 : 5 : 0
b, R_1 = Ph	95 : 1 : 4.5 : 5

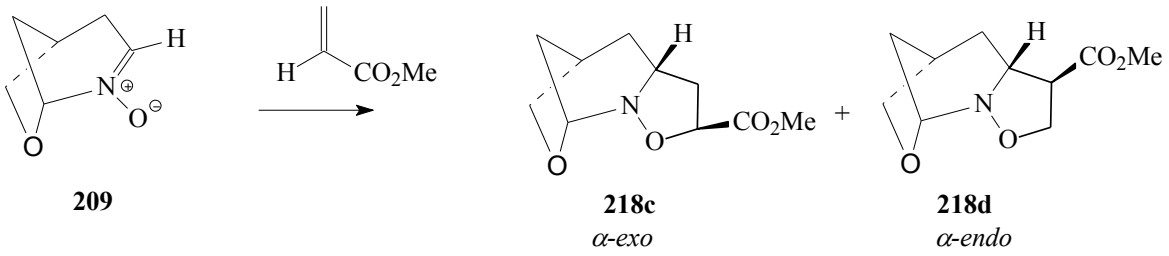
	219 / 221 / 223 / 225
a, R_1 = Ph	4 : 0 : 95 : 1

Scheme 57.

The last reaction is the cycloaddition of nitrone **210** with styrene **141b** as an example to examine the face selectivity (Scheme 58). It was surprising that the major isomer was in agreement with the major isomer from the previous work. This is happened may be due to the effect of the two methyl groups in which they are increasing the crowdness of the α-face over the β-face of the nitrone **210** (Scheme 58).

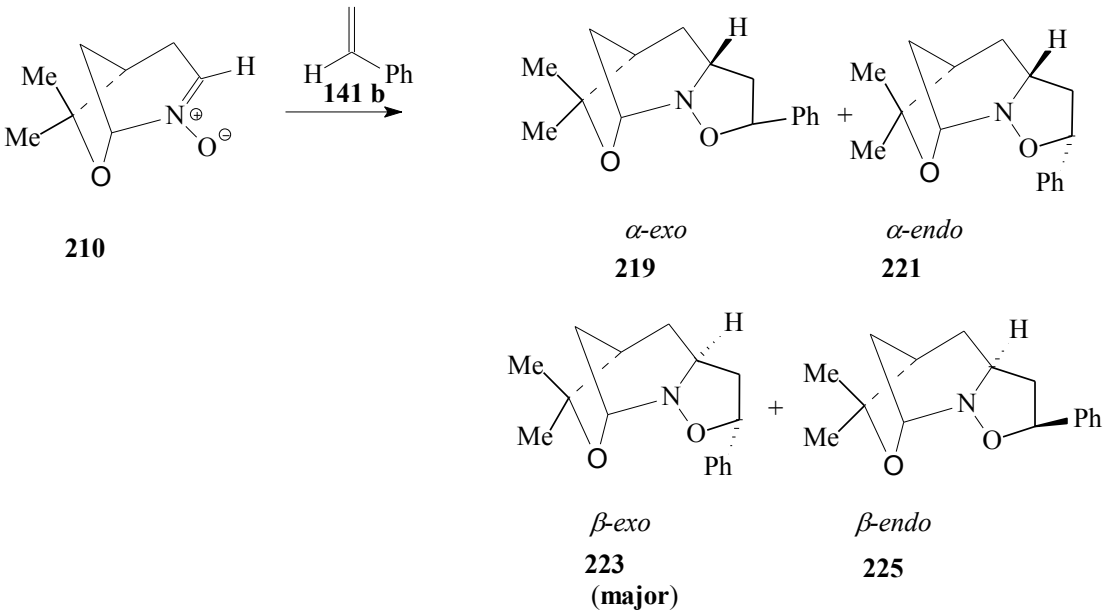

CO2Me
Me
153
H
N
O
O
209
CO2Me
Me
226
227
LiAlH4
OH
CH2OH
228
229
MeCO2
154
218
R1
144
a, R1 = Bu
b, R1 = Ph

Scheme 58.



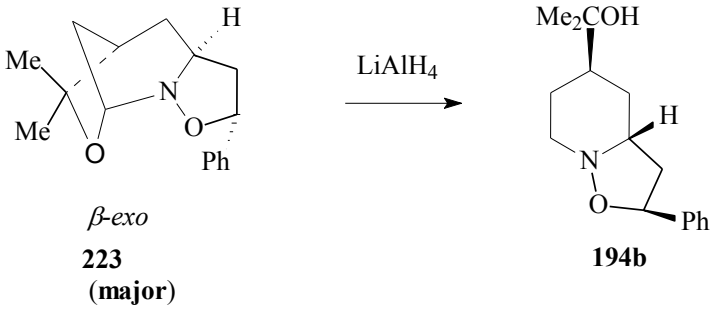
209 **218c** *α-exo* **218d** *α-endo*

Scheme 59.



210 *α-exo* **219** *α-endo* **221**

β-exo **223** (**major**) *β-endo* **225**



β-exo **223** (**major**) **194b**

Scheme 60.

6.3 Experimental

6.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTI.R spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at +25°C using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). 4-methoxycarbonylpiperidine (**187**), 1-hexene, styrene, methyl methacrylate, from Fluka Chemie AG (Buchs, Switzerland) were used as received. All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N_2.

6.3.1. 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxide (209) (210).

To a solution of the hydroxylamine **181** or **139** (0.796 g, 5.0 mmol) in dry $CHCl_3$ (50 mL) was added yellow HgO (4.3 g, 20 mmol) and the mixture was stirred using a magnetic stir bar at 20°C for overnight or until the oxidation was complete (as indicated by TLC experiment in ether). The mixture was then filtered through a bed of celite and $MgSO_4$. After removal of the solvent, the bicyclic nitrone **210** was obtained as a solid in almost quantitative yield, while the bicyclic nitrone **209** was used directly. Mp 87-89°C of **210** (ether); (Found: C, 61.7; H, 8.3; N, 8.9. $C_8H_{13}NO_2$ requires C, 61.91; H, 8.44; N, 9.03%.); ν_{max} (KBr) 3296, 2972, 2937, 1642, 1605, 1451, 1369, 1303, 1195, 1176, 1142, 1117, 1088, 1059, 1032, 963 and 899 cm^{-1}; δH (500 MHz, $CDCl_3$, +25°C) 6.82-6.79

(1H, m), 5.18 (1H, d, *J* 3.5 Hz), 2.66-2.48 (3H, m), 2.40-2.36 (1H, m), 2.21 (1H, d, *J* 12.3 Hz), 1.38 (3H, s), 1.30 (3H, s); δC (500 MHz, $CDCl_3$, +25°C) 130.2, 98.0, 85.3, 38.2, 34.5, 28.9, 28.6, 24.6.

6.3.2. Reaction of nitrone 209 with 1-hexene (141a)

To a stirring solution of the hydroxylamine **139** (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100mg) in 10 min. The reaction mixture was then stirred at room temperature for 6 h. The mixture was filtered over a bed of magnesium sulphate. The resulting solution was stirred at room temperature overnight after which 1-hexene **141a** was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the adduct as a colorless liquid (0.25 g, 40%).

ν_{max} (neat) 2928, 2871, 1448, 1379, 1303, 1221, 1062, 984, 908, 866, 788, 728 and 645 cm^{-1}. δH (500 MHz, $CDCl_3$, +25°C) 5.12- 5.11 (1H, d, J 5.5 Hz), 4.48- 4.43 (1H, m), 3.86-3.84 (1H, d, 8.3 Hz), 3.73-3.71 (1H, m), 3.57- 3.51 (1H, q, J 9.5 Hz), 2.45-2.40 (1H, m), 2.37-2.27 (1H, m), 2.17-2.11 (1H, m), 1.99-1.95 (1H, td, J 2.4, 14.0 Hz), 1.90-1.80 (3H, m), 1.57-1.50 (1H, m), 1.44-1.26 (5H, m), 0.89 (3H, t, J 7.1 Hz) ; δC (500 MHz, $CDCl_3$, +25°C) 93.1, 81.0, 72.2, 55.9, 41.6, 36.7, 35.5, 33.1, 30.4, 28.0, 22.7, 14.0.

6.3.3. Reaction of nitrone 209 with styrene (141b)

To a stirring solution of the hydroxylamine **139** (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100mg) in 10 min. The reaction mixture was then stirred at room temperature for

6 h. The mixture was filtered over a bed of magnesium sulphate. The resulting solution was stirred at room temperature overnight after which styrene 141b was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the adduct as white solid 218b Mp 116-118 °C (0.28 g, 45%). M+ 231.1; ν_{max} (KBr disc) 2987, 2928, 2872, 1489, 1446, 1360, 1309, 1281, 1216, 1087, 1070, 1015, 978, 915, 830, 806, 761, 726, 695 and 674 cm^{-1}. δH (500 MHz, $CDCl_3$, +25°C) 7.35-7.23 (5H, m), 5.50-5.47 (1H, dd, J 4.6, 9.5 Hz), 5.25- 5.24 (1H, dd, J 1.5, 4.6 Hz), 3.94-3.92 (2H, d, 8.2 Hz), 3.81-3.75 (1H, m), 2.75- 2.68 (1H, q, J 10.7 Hz), 2.47-2.46 (1H, m), 2.23-2.12 (2H, m), 2.03-2.00 (1H, m), 1.94-1.91 (2H, m) ; δC (500 MHz, $CDCl_3$, +25°C) 143.0, 128.3 (2C), 127.4, 126.2 (2C), 93.2, 82.5, 72.4, 56.4, 45.1, 35.5, 33.1, 30.4.

6.3.4. Reaction of nitrone 209 with methyl methacrylate (153)

A solution of nitrone **209** (3.0 mmol) in chloroform (20 mL) containing methylmethacrylate **(153)** (4 mL) was stirred at room temperature over night under N_2 in a closed vessel. After removal of the solvent and excess alkene the residual crude mixture of cycloadducts was not be able to be purified by chromatography. Then the mixture was taken to the $LiAlH_4$ reduction step (section 6.3.4.).

6.3.5. Reaction of nitrone 209 with methyl methacrylate (153)

To a stirring solution of the hydroxylamine **139** (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100mg) in 10 min. The reaction mixture was then stirred at room temperature for 6 h. The mixture was filtered over a bed of magnesium sulphate. The resulting solution

was stirred at room temperature for four hours after which methyl acrylate (2 ml) was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the the first fraction which contains pure adduct **218d** as a colorless liquid. Continued elution gave the second fraction which contains a pure cycloadducts **218c** as white solid Mp 96-98 °C (0.28 g, 45%).

Compound **218d**

ν_{max} (neat) 2947, 2883, 1741, 1439, 1277, 1206, 908, 726 and 674 cm^{-1}. δH (500 MHz, $CDCl_3$, +25°C) 5.02-5.01 (m, 1H), 4.36-4.32 (m, 1H), 3.97-3.95 (m, 1H), 3.80-3.78 (d, 1H, J= 8.5 Hz), 3.70-3.69 (m, 1H), 3.68 (s, 3H), 3.67-3.64 (m, 1H), 3.36-3.34 (m, 1H), 2.40-2.38(m, 1H), 2.12-2.10(m, 2H), 1.82-1.80 (m, 2H) ; δC (500 MHz, $CDCl_3$, +25°C) 172.9, 92.9, 72.2, 72.1, 60.2, 53.1, 51.9, 35.2, 32.6, 29.5.

Compound **218c**

ν_{max} (KBr disc) 2949, 2885, 1740, 1438, 1276, 1203, 1068, 1029, 911, 726 and 698 cm^{-1} .δH (500 MHz, $CDCl_3$, +25°C) 5.05-5.03 (m, 1H), 4.83-4.80 (m, 1H), 3.76-3.72 (m, 1H), 3.68-3.66 (m, 1H), 3.65 (s, 3H), 3.55-3.53 (m, 1H), 2.52-2.50 (m, 1H), 2.39-2.37 (m, 1H), 2.28-2.25 (m, 1H), 2.14-2.10 (m, 1H), 1.98-1.94 (m, 1H), 1.79-1.75 (m, 2H) ; δC (500 MHz, $CDCl_3$, +25°C) 172.0, 92.4, 77.6, 72.1, 55.2, 51.8, 39.9, 34.7, 32.2, 29.7.

3.3.6. Lithium aluminium hydride reduction of cycloadducts 226 and 227 to 228 and 229

To a stirred solution of adducts **226** and **227** (from section 6.3.3) (100 mg, 0.33 mmol) in ether (15 mL) was added lithium aluminium hydride (100 mg, 2.7 mmol) at room temperature. The reaction was complete in 10 min as indicated by TLC experiment (silica, ether). To the reaction mixture was added water (0.1 g), 10% NaOH solution (0.1 g) and water (0.4 g). The mixture was stirred for 1 h and was then decanted and the residue washed with CH_2Cl_2. The organic layer was dried (Na_2SO_4), concentrated, and purified by silica gel chromatography using a 85:15 ether/methanol as the eluant to give **228** as colourless liquid (71 mg, 92%), then continuing elution gave **229** as a white liquid**.**

6.3.7. Lithium aluminium hydride reduction of cycloadduct 154 and 229

Major invertomer 229

ν_{max} (KBr disc) 3411, 2966, 2935, 2859, 1448, 1385, 1324, 1119, 1044, 975, 912, 793, and 730 cm^{-1}. δH (500 MHz, $CDCl_3$, +25°C) 3.78-3.75 (1H, m), 3.62-3.52 (2H, m), 3.42-3.41 (3H,m), 2.562.41 (2H, m), 2.04-1.99 (1H, m), 1.96- 1.94 (2H, m), 1.88-1.83 (1H, m), 1.74-1.66 (2H, m), 1.57-1.53 (2H, m), 1.25 (3H, s), 1.23-1.93 (1H, m) ; δC (500 MHz, $CDCl_3$, +25°C) 23.0, 25.5, 29.8, 33.6, 42.6, 50.9, 62.2, 62.7, 66.6, 80.7.

Minor invertomer 229

δC (500 MHz, $CDCl_3$, +25°C) 24.5, 27.7, 28.4, 32.9, 37.4, 51.6, 59.3, 68.5, 70.1, 86.4.

6.3.8. Lithium aluminium hydride reduction of cycloadducts 218a,b to 144a,b

A sample of adduct **218a,b** was reduced with $LiAlH_4$ using procedure as described above to give **144a,b** as a coluorless liquid (93% yield)**,** which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 4.3.4.2. and 4.3.5.3.

6.3.9. Reaction of nitrone 210 with styrene (141b)

To a stirring solution of the hydroxylamine 181 (0.39 g, 3 mmol) in chloroform (20 mL) was added yellow mercuric oxide (0.65 g, 12 mmol) and anhydrous magnesium sulphate (100mg) in 10 min. The reaction mixture was then stirred at room temperature overnight. The mixture was filtered over a bed of magnesium sulphate. The resulting solution was stirred at room temperature overnight after which styrene 141b was added under nitrogen. After that, the reaction mixture was concentrated and the residual liquid was chromatographed over silica using 10% ether: methanol mixture as an eluant to give the adduct as yellow liquid **223a** (0.28 g, 45%). νmax (neat) 2970, 2932, 2865, 1448, 1368, 1272, 1181, 1130, 1101, 1036, 1004, 907, 823, 727, 699 and 644 cm^{-1}. δH (500 MHz, $CDCl_3$, +25°C) 7.42-7.24 (5H, m), 5.23- 5.20 (1H, m), 5.14- 5.11 (1H,m), 4.02-3.97 (1H, m), 3.81-3.75 (1H, m), 2.43- 2.41 (1H,m), 2.23-1.95 (4H, m), 1.61-1.56 (1H, m), 1.48 (3H, s), 1.25 (3H, s) ; δC (500 MHz, $CDCl_3$, +25°C) 140.8, 128.4 (2C), 127.7, 126.7 (2C), 90.1, 83.1, 78.5, 54.8, 44.9, 39.9, 32.9, 31.8, 29.3 (2C).

6.3.10. Lithium aluminium hydride reduction of cycloadduct 223 to194b

A sample of adduct **223** was reduced with $LiAlH_4$ using procedure as described above to give **194a** as a white solid (93% yield)**,** which is identical in every respect to that obtained by cycloaddition reaction as mentioned in Section 5.3.7.

CHAPTER 7

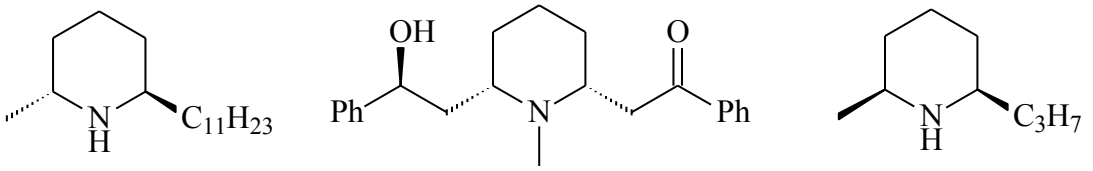
A short stereoselective synthesis of racemic 2-epicalvine

Summary:

The cycloaddition reaction of 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide with butyl vinyl ether was used as a key step in the short stereoselcetive racemic synthesis of ladybird beetle alkaloid 2-epicalvine. The cycloadduct on quartenization with 2-bromoethanol followed by ring openinng and lactonization afforded the natural product in a single pot reaction.

7.1 Introduction

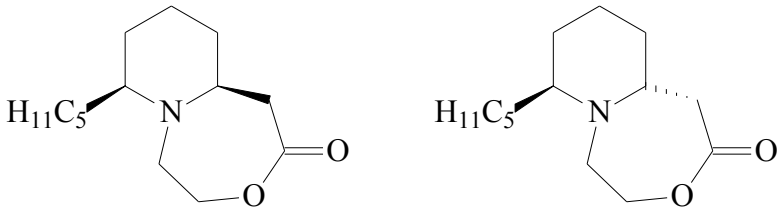
Substituted piperidines are abundant in nature and many of these exhibit important biological activities. Particularly 2,6-disubstituted piperidines are one of the most common piperidine skeletons and have been the subject of intensive studies and synthetic efforts.[102] One renowned example of this family is solenopsin A, the active ingredient in fire ants Solenopsis, which shows cytotoxic, hemolytic, necrotic, insecticidal, antibacterial, and antifungal activities [103]. Two examples of 2,6-disubstituted piperidines found in plants are lobeline from Indian tobacco *(Lobelia inflata*) [104] and dihydropinidine from pines, which was found later in the Mexican bean beetle (*Epilachna varivestis*) [105].



(-)- Solenopsin A (-)- Lobeline (-)- Dihydropinidine

Figure 10.

Ladybird beetles (*Coccinellidae)* are rarely exploited as food sources by predators, owing to toxic alkaloids produced in their hemolymph, which are released as yellow small droplets from their knee joints once they are disturbed or molested [106]. Calvine, a *cis*-2,6-disubstituted piperidine annulated with a seven-membered lactone, is the major alkaloid found in two ladybird beetles *Calvia 10-guttata* and *Calvia 14-guttata.* 2-Epicalvine, its corresponding trans-lactone was also found as the minor constituent (about 10%). Braekman et al. isolated the alkaloids in 1999 and determined their absolute configuration by enantioselective syntheses in 2000 [107].



(+)- calvine (+)- 2-epicalvine

Figure 11.

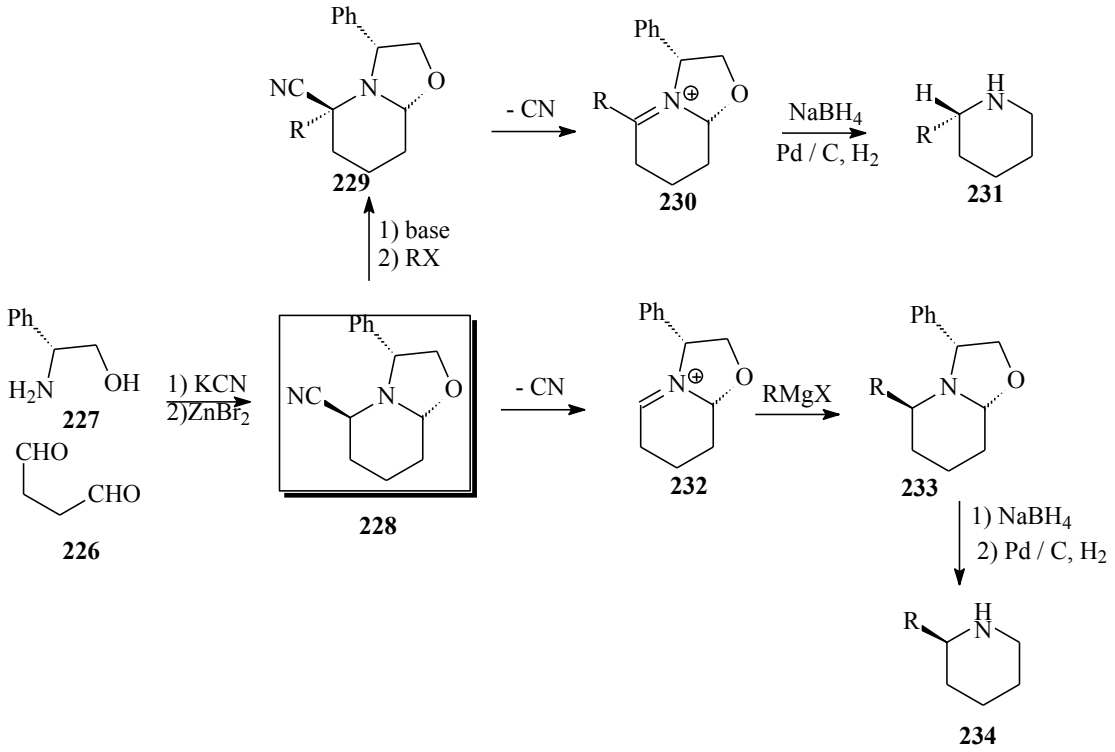
7.1.1 Synthetic Strategies of Calvine

So far, four total synthesis syntheses of calvine have been reported. The first synthesis was done by Braekman *et al.* with CN(R,S) method as key step. Troin *et al.*

reported a formal synthesis, which involved an intramolecular Mannich reaction. The third is based on an olefin cross-metathesis (CM) reaction of a chiral homoallylamine and an enone. And the last report is based on the intramolecular Pd(II)-catalysed carbonylation of aminoalkenitol.

7.1.1.1 CN(R,S) Methodology

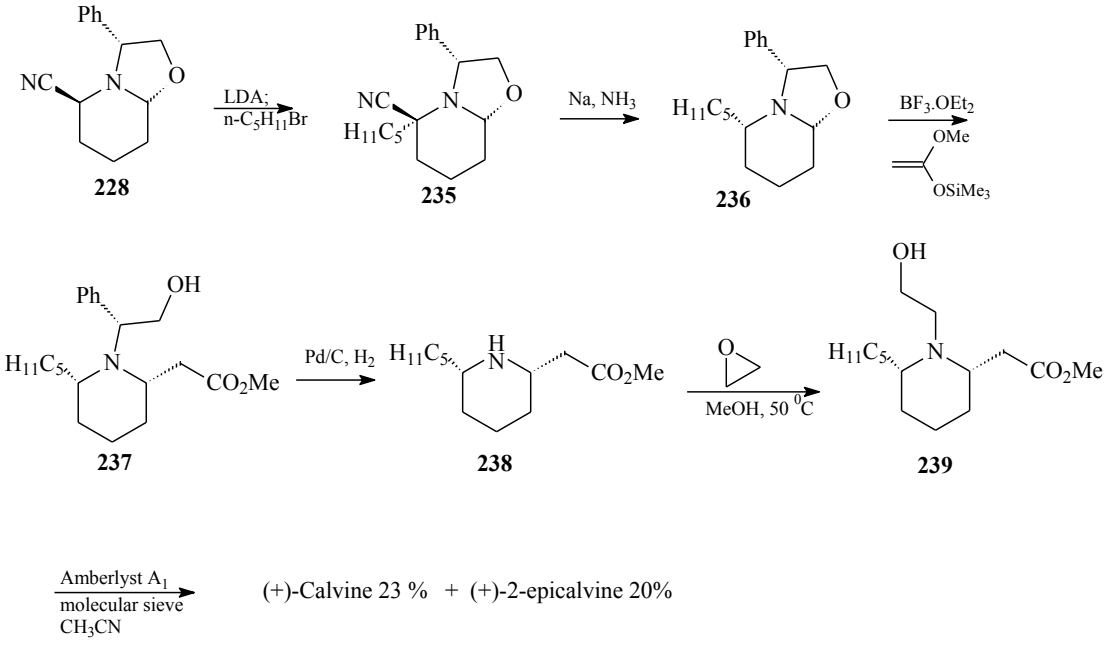
Husson and Royer developed a methodology known as CN(R,S), which based on a chiral Ncyanomethyloxazolidine intermediate. This method is flexible and allows the preparation of piperidines in both R- and S-configurations (Scheme 61) [108].



Scheme 61.

Condensation of glutaraldehyde **226** and phenyl gylcinol **227** in the presence of KCN furnished the Ncyanomethyloxazolidine **228**. Its deprotonation and alkylation affords **229**, which after elimination of the cyano group gives the prochiral iminium **230**.

Reduction and cleavage of the chiral moiety yield the piperidine **231**. On the other hand, elimination of the cyano group from **228** yields the prochiral iminium ion **232**, which reacts with a Grignard reagent to afford **233**. Cleavage of the chiral moiety leads to **234**, the enantiomer of **231**. The method was successfully applied, for example to synthesize both configurations of coniine [109].



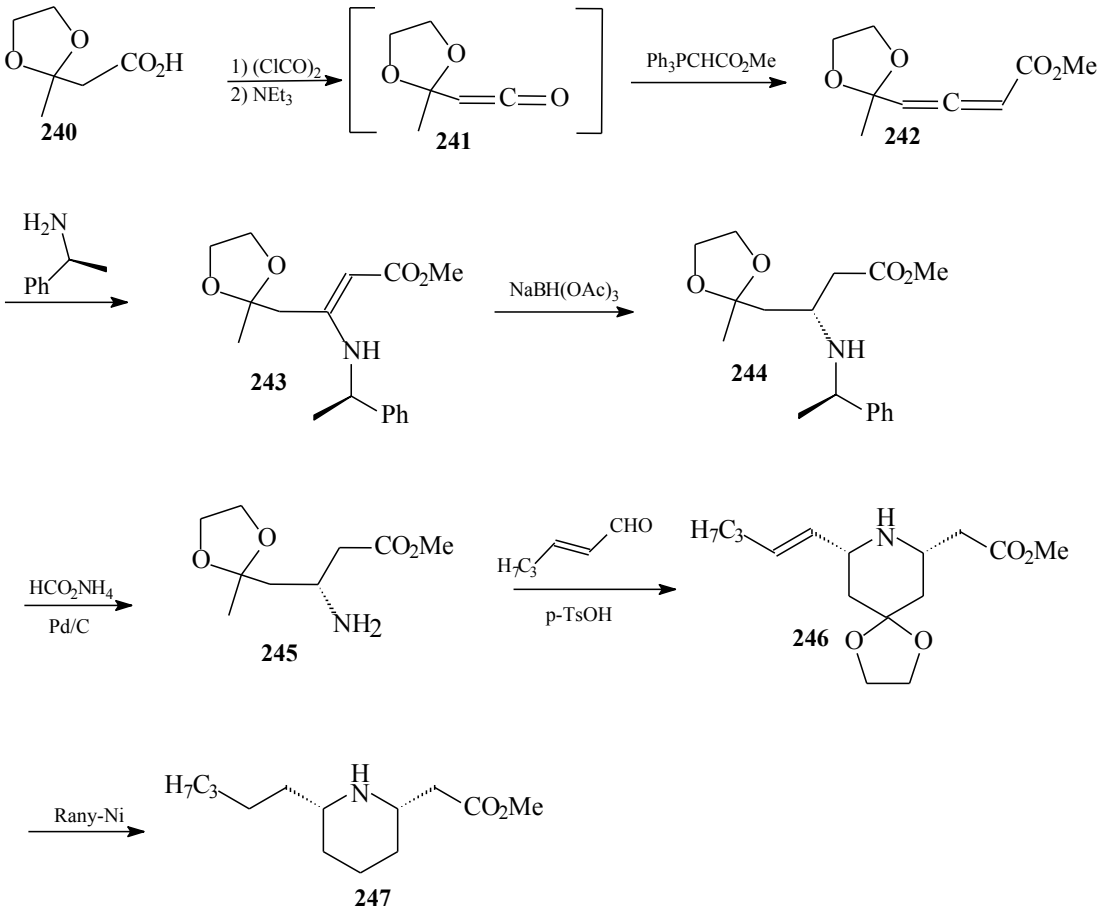
Scheme 62.

The total synthesis of calvine by Braekman *et al.* is outlined in (Scheme 62) [107]. The CN(R,S) method furnished the aminoalcohol **236** after decyanation by sodium in liquid ammonia. Reaction of **236** with 1-methoxy-1-trimethylsilyloxyethene in the presence of $BF_3.OEt_2$ led to piperidine **237** as single isomer [110]. Hydrogenolysis of the chiral appendage afforded the piperidine **238**. Introduction of the ethylhydroxyl group was conducted by treating **238** with an excess of ethylene oxide in methanol, which resulted in a crude mixture containing calvine, epicalvine, methylester **239** (*cis:trans* 1:1). Subjecting the crude product mixture to the lactonization conditions in the presence of Amberlyst A15

and molecular sieves in acetonitrile yielded calvine, epicalvine in 23, 20 yield, respectively. The major drawback of the synthesis is the hydroxyethylation reaction, which gave low yield and selectivity. However, it was essential to prepare both calvine and 2-epicalvine for determination of their structures.

7.1.1.2. Intramolecular Mannich Reaction

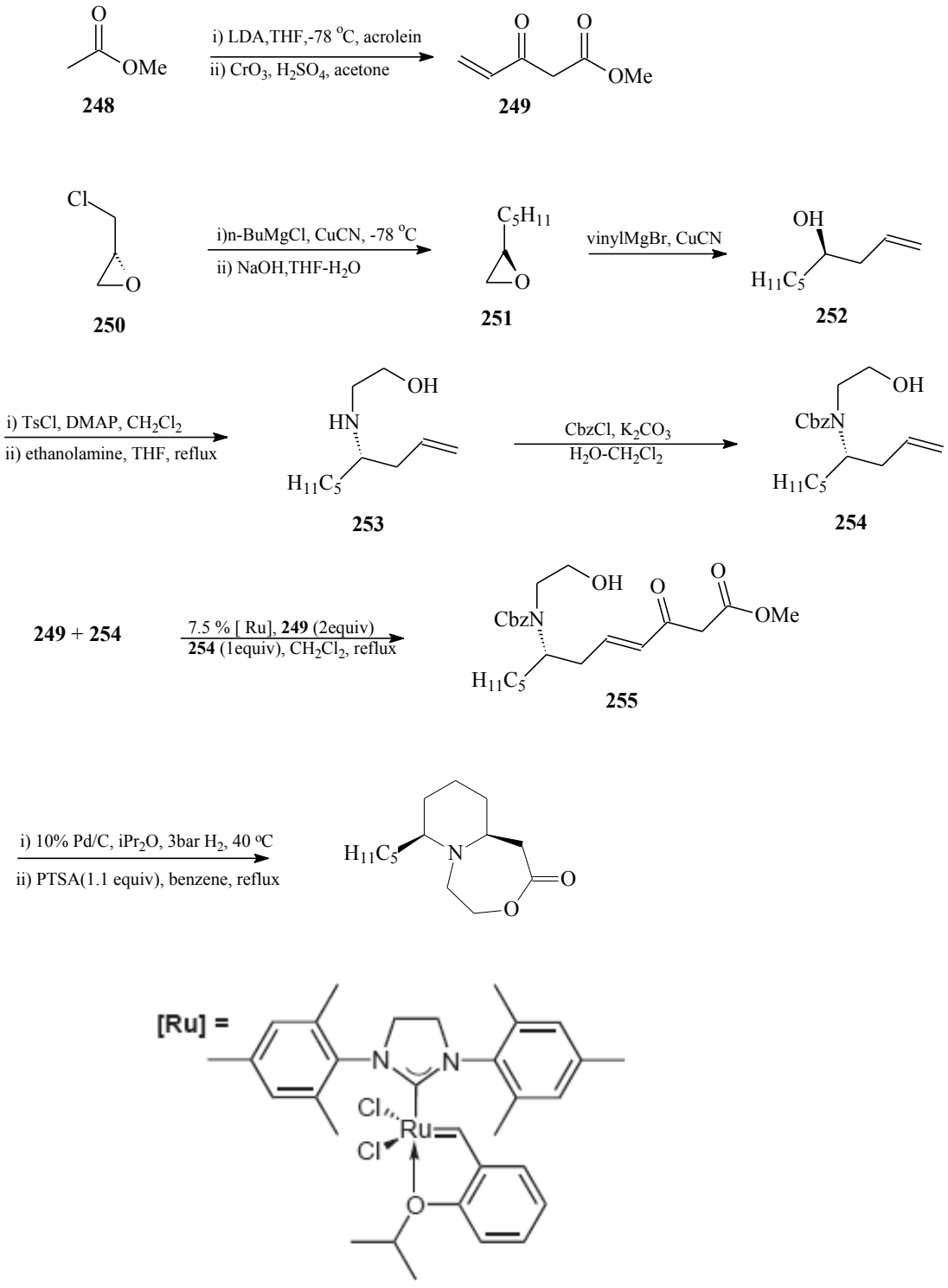
Troin *et al*. reported the synthesis of piperidine **247** from a chiral -aminoester **245** and hex-2- enal via Mannich-type reaction as shown in (Scheme 63) [111]. The preparation of the aminoester started from acid **240**, which was transformed to the acylchloride. Treatment of the crude mixture with triethylamine and methyl triphenylphosporanylidene acetate gave the conjugated allenic ester **242** *via* ketene intermediate **241** and subsequent Wittig reaction. Nucleophilic addition of (R)-methylbenzylamine provided an inseparable 3:1 *Z/E* mixture of chiral enaminoester **243**. The *Z*-isomer, which was stabilized by intramolecular hydrogen bond, formed predominantly [112]. Reduction of the product with sodium acetoxyborohydride yielded amine **244** (dr 75:25), which was readily separated from its diastereomer. Hydrogenation led to the chiral aminoester **245**, which reacted with hex-2-enal to give **246**. Transformation of the dioxolane to dithiolane derivative followed by the reaction with Raney nickel furnished the piperidine **247**. The synthetic route was lengthy and with moderate selectivity in the nucleophilic addition reaction.



Scheme 63.

7.1.1.3. Olefin cross-metathesis (CM) reaction of a chiral homoallylamine and an enone.

Blechert *et.al.* apply the sequential olefin cross-metathesis–reductive cyclization method to synthesize calvine[113]. In contrast to the synthesis of Braekman, he found it advantageous to introduce the hydroxyethyl group early in the synthesis to avoid the unselective hydroxyethylation(scheme 64). Compound **249** was prepared in two steps according to the procedure of Zibuck and Streiber [114]. The Jones oxidation yielded the desired enone **3** in 55% yield.



Scheme 64.

The homoallyalamine **254** was prepared in six steps, starting from (*R*)-epichlorohydrine **250**. Its conversion to pentyl Oxirane **251** was done by copper-catalyzed

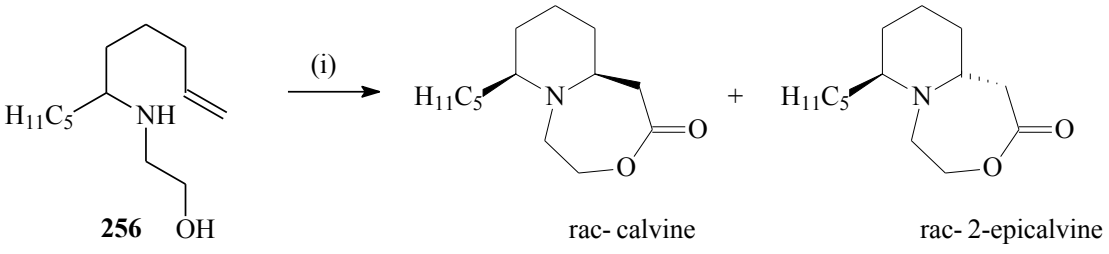
oxirane opening with *n*-butyl magnesium chloride followed by oxirane formation in basic conditions [115]. The transformation of homoallylalcohol **252** to homoallylamine **254** was accomplished by tosylation, nucleophilic substitution, and introduction of the Cbz protecting group, yielding the homoallylamine **254**.

CM between enone **249** and homoallylamine **254** was conducted in the presence of 7.5 mol% Hoveyda–Blechert ruthenium catalyst [Ru] [116]to afford exclusively the *E*-enone **255** in 70% yield. The catalyst was chosen as it shows higher reactivity and stability than the second generation Grubbs' catalyst [117].

Reductive hydrogenation in isopropyl ether at 3 bar of hydrogen and 40 °C for three days followed by treatment with a slight excess of *p*-toluenesulfonic acid in refluxing benzene to afford neat calvine in 66% yield.

7.1.1.4. Intramolecular Pd(II)-catalysed carbonylation of aminoalkenitol

Szolcsanyi *et. al.* report a short racemic syntheses of the alkaloids calvine and epi-calvine featuring Pd(II)- catalysed aminocyclisation–lactonization [118] as a key step (Scheme 64).



Scheme 65. (i) CO (balloon), 0.1 equiv. $PdCl_2$, 2equiv. $CuCl_2$, 2 equiv. AcONa, dioxane , 40 ^oC, 7h, (55 %, 2.2:1)

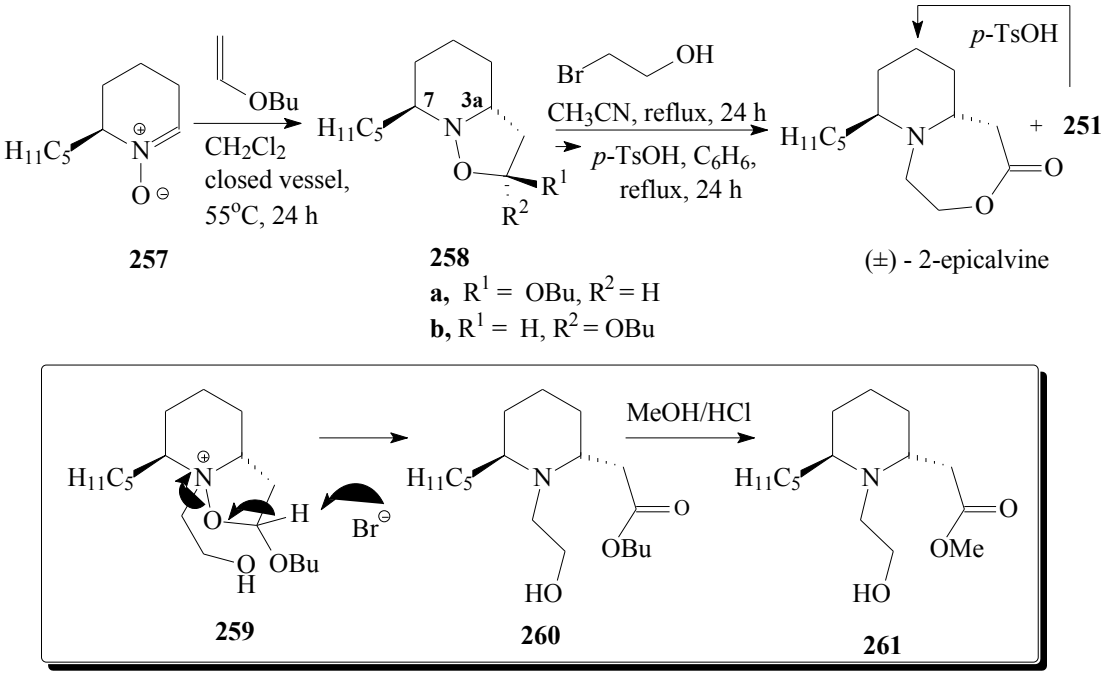
After some experimentation, they identified the optimal catalytic system consisting of $PdCl_2$ as catalyst, excess $CuCl_2$ and AcONa as reoxidant and base, respectively. These reaction conditions which involved heating in dioxane under a CO atmosphere afforded racemic calvine rac-1 and epicalvine rac-2 in 55% combined yield and in the ratio 2.2:1 (Scheme 65).

Its worth to mention that all the reported syntheses, the *cis*-lactone (Calvine) is formed either as the predominant or sole isomer. So far, no stereoselective synthesis of the trans- lactone (2-epicalvine) has been reported. Also its noted that the over all yield in the previous syntheses are very low. Herein, we report a concise stereoselective racemic synthesis of the alkaloid 2-epicalvine via nitrone cycloaddition reaction as a key step.

7.2 Results and Discussion

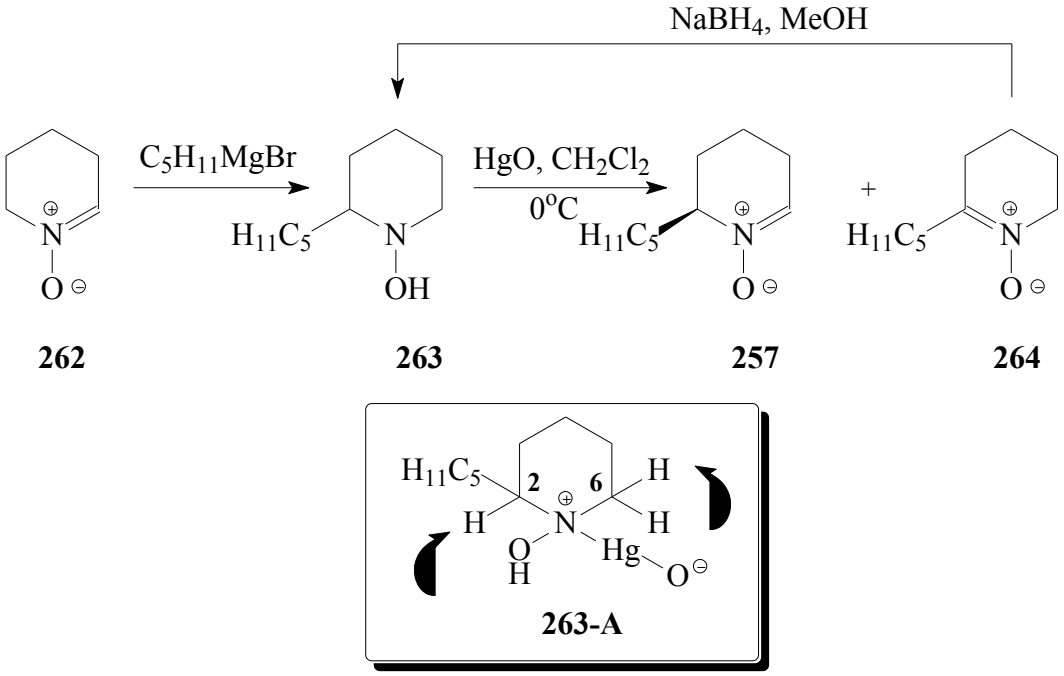
Nitrone (**257**)-butyl vinyl ether cycloaddition reaction at 50°C afforded a mixture of stereoisomers **258a** and **258b** in 92 % yield in a respective ratio of 85:15 in a face selective manner; substituent at C(6) in cyclic nitrones are known to force alkenes to approach exclusively from its sterically favourable α-face (Scheme 66) [114]. Similar stereoselectivity is documented in the addition reaction of parent 5- or 6-membered cyclic nitrones with ethyl vinyl ether [119]. The trans stereochemistry of the substituents at C(3a) and C(7) in **258a** or **258b** is assured by the subsequent transformation of the cycloadducts to 2-epicalvine . In a single pot reaction, quaternization of adduct **258a** with 2-bromoethanol to **259**, followed by bromide catalyzed ring opening [120] to **260** and lactonization afforded the natural product 2-epicalvine in 46% yield and the uncyclised alcohol ester **260** (26% yield). Likewise, the adduct **258b** was also converted into 2-

epicalvine, thereby confirming the trans relationship of the substituents. Note that the spectral analyses failed to detect the presence of the isomeric natural product calvine. However, when the above lactonization was repeated in refluxing toluene instead of benzene, a mixture of Calvine and 2-epicalvine was obtained in a respective ratio of 1:2 (56% yield) along with uncyclised alcohol **260** (11%). At the higher temperature, isomerization happened via retro-Michael and Michael reactions involving β-amino ester functionalities [107]. In a separate experiment, the intermediate **260** was isolated and converted into 2-epicalvine by p-tosic acid catalyzed lactonization. The identity of the intermediate **260** was confirmed by its conversion to the known methyl ester **261** (Scheme 64) [107]. The methodology described above can be applied to incorporate and elaborate piperidine moiety so widespread in nature. Also note that this is the first stereoselective synthesis of the trans compound 2-epicalvine (all other reported syntheses led to the *cis* isomer 1).



Scheme 66.

Regiochemical complication associated with the generation of 6-substituted-3,4,5,6-tetrahydropyridine 1-oxide like **257** is a long standing problem and remains so at this stage [114a,122]. Our repeated attempts to generate the nitrone by mercury(II) oxide oxidation of 2-pentyl-N-hydroxypiperidine **263** resulted in a mixture of aldonitrone **257** and ketonitrone **264** in a respective ratio of 29:71 in almost quantitative yields (Scheme 67). Attempts to influence the abstraction of the C(6)H by carrying out the oxidation process using mercury(II) oxide or p-benzoquinone in CH_2Cl_2 in the presence of 1 equivalent of bulky base Et_3N or in solvent like t-butanol did not improve the ratio in favour of the desired aldonitrone **257**. However, the regiochemical problem is partially solved by recycling the ketonitrone **264** to aldonitrone **257** via $NaBH_4$ reduction followed by mercury (II) oxide oxidation.



Scheme 67.

7.3 Experimental

7.3.1. General

Elemental analysis was carried out on a Perkin Elmer Elemental Analyzer Series 11 Model 2400. IR spectra were recorded on a Perkin Elmer 16F PC FTI.R spectrometer. ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ at +25°C using TMS as internal standard on a JEOL LA 500 MHz spectrometer. Mass spectra were recorded on a GC/MS system (Agilent Technologies, 6890N). Silica gel chromatographic separations were performed with Silica gel 100 from Fluka Chemie AG (Buchs, Switzerland). All solvents were of reagent grade. Dichloromethane was passed through alumina before use. All reactions were carried out under N_2.

7.3.2. 2-pentyl-N-hydroxypiperidine 263

Prepared by dropwise addition of pentylmagnesium bromide (55 mmol) in ether (100 mL) to a solution of nitrone **262 [**120a] (50 mmol) in (100 mL) at 20°C. After stirring for 1 h a saturated solution of NH_4Cl (100 mL) was added to the reaction mixture and extracted with diethyl ether (2 × 50 mL). Colourless liquid, 82%, $bp_{0.8\ mbarHg}$100°C; ν_{max} (neat) 3210, 2935, 2853, 1455, 1377, 1355, 1260, 1229, 1177, 1103, 1064, 1035, 986, 949, 862, 828, 775 and 729 cm^{-1}; δH (500 MHz, $CDCl_3$, +25 °C) 7.24 (1H, br, OH), 3.30 (1H, apparent d, J 10.1 Hz), 2.49 (1H, ddd, J 3.0, 10.3, 13.1 Hz), 2.27-2.20 (1H, m), 2.04-1.95 (1H, m), 1.87-1.82 (1H, m), 1.75-1.50 (3H, m), 1.40-1.10 (9H, m), 0.89 (3H, t, J 7.0 Hz); δC (125 MHz, $CDCl_3$, +25 °C) 67.8, 59.7, 33.2, 32.3, 31.0, 25.9, 25.5, 23.8, 22.7, 14.1.

7.3.3. Reaction of nitrone 257 with butyl vinyl ether

A mixture of hydroxylamine **263** (3.80 g, 22 mmol) in CH_2Cl_2 (75 mL) and HgO oxidation (13 g, 60 mmol) was stirred at 0-10°C for 4h or until the TLC experiment (silica, ether) indicated the completion of the reaction. After filtering through a bed of $MgSO_4$, the solution of the nitrones **257** and **264** was reacted with butyl vinyl ether (15 mL) in a closed vessel at 55ºC for overnight. Chromatography of the crude products over silica gel using 9:1 hexane /ether as eluant to give the minor isomer **258b** (40 mg) as a colorless liquid. Continued elution gave a mixture of two adducts (650 mg) then finally the major adduct **258a** as a colorless liquid (900 mg). The total isolated yield of adducts **258a** and **258b** was thus found to be 27% (92% based on the nitrone **257**. Continued elution with 1:1 ether/methanol gave the ketonitrone **264** (2.5 g, 67%).

7.3.3.1. 2-butoxy-7-pentyl-hexahydro-2H-isoxazolo[2,3-a]pyridine 258a

ν_{max} (neat) 2954, 2930, 2862, 1462, 1447, 1352, 1250, 1193, 1123, 1088, 943, 909, 849, 821 and 730 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 5.27 (1H, d, *J* 4.8 Hz), 3.74 (1H, td, *J* 6.7, 9.5 Hz), 3.77-3.67 (1H, m), 3.36 (1H, td, *J* 6.7, 9.2 Hz), 2.54-2.45 (1H, m), 2.40-2.30 (1H, m), 1.97-1.70 (5H, m), 1.54 (2H, quint, *J* 7.0 Hz), 1.52-1.46 (1H, m), 1.40-1.10 (11 H, m), 0.90 (3H, t, *J* 7.3 Hz), 0.88 (3H, t, *J* 7.0 Hz); δ_C (125 MHz, $CDCl_3$, +25 °C) 102.5, 67.6, 60.9, 57.5, 37.4, 33.9, 32.1, 31.7, 28.8, 25.2 (2C), 22.6, 19.3, 18.6, 13.9 (2C).

7.3.3.2. 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide 264

mp 133-135 °C (Et_2O/CH_2Cl_2); ν_{max} (KBr) 3415, 2955, 2931, 2869, 1656, 1630, 1448, 1379, 1333, 1282, 1248, 1195, 1150, 1068, 956 and 892 $cm._{-1}$. δH (500 MHz, $CDCl_3$, +25 °C) 3.85-3.77 (2H, m), 2.57-2.50 (2H, apparent t, J 7.6 Hz), 2.46-2.40 (2H, m), 1.93 (2H, dquint, J 2.5, 6.1 Hz), 1.74 (2H, dquint, J 2.5, 6.1 Hz), 1.58-1.51 (2H, m), 1.38-1.30 (4H, m), 0.90 (3H, t, J 7.0 Hz); δC (125 MHz, CDCl3, +25 °C) 149.4, 58.0, 31.8, 31.5, 28.6, 24.1, 23.0, 22.3, 18.6, 13.8.

7.3.2. Reaction of cycloadducts 258a with 2-bromoethanol to form epi-calvine

A mixture of adduct **258a** (2.0 mmol), 2-bromoethanol (2.3 mmol) in acetonitrile (10 cm3) was refluxed under N_2 for 24 h. After adding p-TsOH.H_2O (2.0 mmol), acetonitrile was exchanged with dry benzene (30 cm^3). The solution was then refluxed for a further 24 h. After removal of benzene the reaction mixture was diluted with CH_2Cl_2 (40 cm^3); the organic layer was washed with 5% K_2CO_3 solution (15 cm^3). The aqueous layer

was re-extracted with CH_2Cl_2 (15 cm^3). The combined organic layers was dried, concentrated, and the residual liquid was chromatographed over silica using 9:1 ether/ hexane to give the uncyclised alcohol **260** as a colorless liquid (160 mg, 26%). Continued elution with 95:5 ether/methanol saturated with NH_3 gave (±)-2-epicalvine (220 mg, 46%).

7.3.2.1. Epi-calvine

ν_{max} (neat) 2927, 2860, 1727, 1652, 1465, 1434, 1374, 1309, 1280, 1244, 1218, 1168, 1059, 1028, 939, 894, 743, and 596 cm^{-1}; δH (500 MHz, $CDCl_3$, +25 °C), 4.34 (1 H, dd, J 8.5, 13.3 Hz), 4.23 (1 H, dd, J 6.1, 13.3 Hz), 3.01 (1H, dd, J 6.1, 14.6 Hz), 2.96 (1H, dd, J 8.5, 14.6 Hz), 2.87 (1H, apparent t, J 9.8 Hz), 2.75 (1H, dd, J 9.8, 13.7 Hz) , 2.78-2.72 (1H, overlapping m), 2.53 (1H, d, J 13.7 Hz), 1.70-1.10 (14H, m), 0.89 (t, 3H , J 7.0 Hz); δC (125 MHz, $CDCl_3$, +25 °C) 174.2, 68.5, 60.6, 54.8, 51.1, 42.9, 32.4, 31.9, 26.8, 26.7, 24.4, 22.5, 18.6, 13.9.

7.3.2.2 Compound 260

ν_{max}(neat)3424, 2954, 2923, 2859, 1727, 1463, 1381, 1352, 1288, 1258, 1176, 1118, 1058, and 727 cm^{-1}; δ_H (500 MHz, $CDCl_3$, +25 °C) 4.13- 4.02 (2H, m), 3.57 (1H, ddd, *J* 3.7, 8.3, 11.8 Hz), 3.44 (1H, td, *J* 4.6, 10.7 Hz), 3.45-3.37 (1H, overlapping m), 3.12 (1H, br OH), 2.81-2.68 (3H, m), 2.59 (1H, td, *J* 4.0, 13.4 Hz), 2.32(1H, dd, *J* 6.4, 15.0 Hz), 1.75-1.18 (14H, m), 1.60 (2H, quint, *J* 7.3 Hz), 1.38 (2H, hext, *J* 7.3 Hz), 0.94 (3H, t, *J* 7.3 Hz), 0.88 (3H, t, *J* 7.3 Hz); δ_C (125 MHz, $CDCl_3$, +25 °C) 172.8, 64.4, 59.5, 54.5, 52.6, 47.1, 37.0, 32.9, 31.9, 30.6, 26.3, 25.5, 24.0, 22.6, 20.4, 19.1, 14.0, 13.7.

Conclusions

Scope and limitation with respect to asymmetric induction in the cycloaddition reactions of several mono- and disubstituted alkenes with a (-)norephedrine-derived methylenenitrone has been investigated.

The cycloaddition reactions of several mono- and disubstituted alkenes with 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide have been found to be highly stereo- and face-selective. The addition reactions have displayed a very high degree of face selectivity (13-48:1). The invertomeric analysis revealed that the bicyclic cycloadducts remain predominantly as the cis-fused isomer which leads to the formation of synthetically important second-generation cyclic aldonitrones via peracid oxidation. The cycloadducts with two equivalents of peracid afforded the cyclic N-hydroxy lactams, presumably via further oxidation of the aldonitrones. The piperidine ring has been elaborated by cycloaddition reaction of the second-generation nitrones with several alkenes, which in most cases gave the cycloadducts in a stereoselective manner.

Likewise, the cycloaddition reactions of 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide with mono- and di-substituted alkenes have been found to be highly stereo- as well as face-selective. The cycloadducts, upon peracid oxidation, leads to the exclusive formation of synthetically important second-generation cyclic aldonitrones.

The treatment of the first generation nitrone i.e., 4-hydroxymethyl-3,4,5,6-tetrahydropyridine 1-oxide or 4-(2-hydroxy-2-propyl)-3,4,5,6-tetrahydropyridine 1-oxide,

with mercury(II) oxide afforded novel bicyclic nitrones, 1-oxa-5,6-dehydro-6-aza-bicyclo[3,2,1]heptane 6-oxides, whose cycloaddition reactions were briefly examined.

The cycloaddition reaction of 6-pentyl-3,4,5,6-tetrahydropyridine 1-oxide with butyl vinyl ether was used as a key step in the short stereoselcetive racemic synthesis of ladybird beetle alkaloid 2-epicalvine.

Overall, the work involved extensive investigation involving cycloaddition reactions of chiral nitrones. The results would indeed be useful in incorporation and elaboration of puiperidine alkaloids so widespread in nature.

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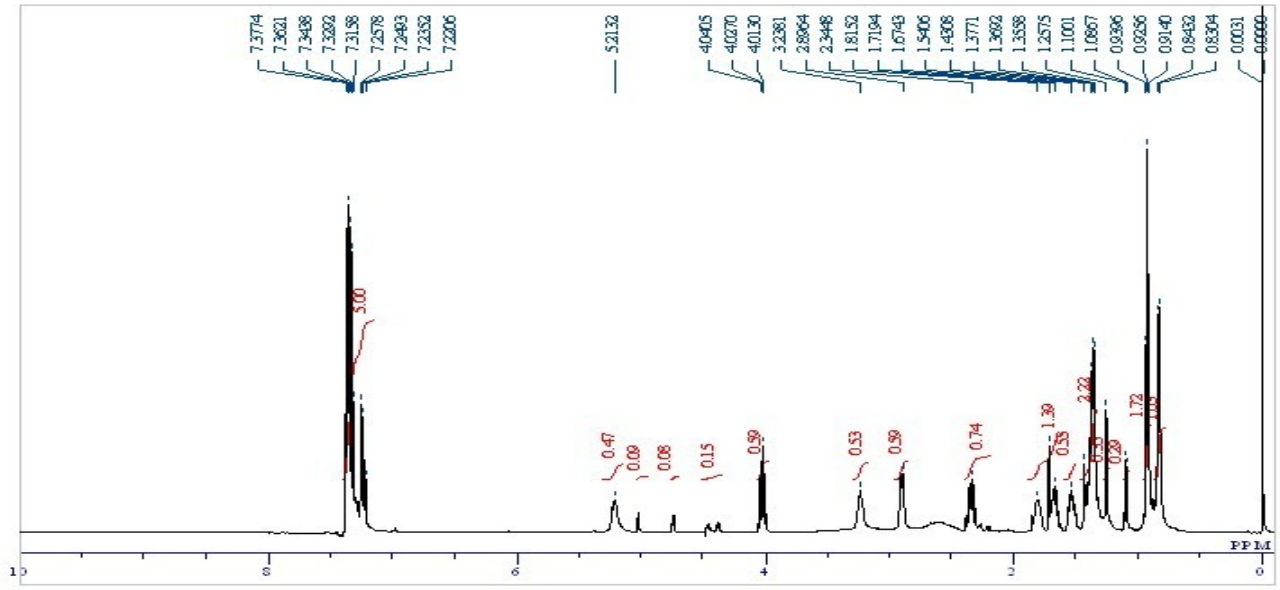
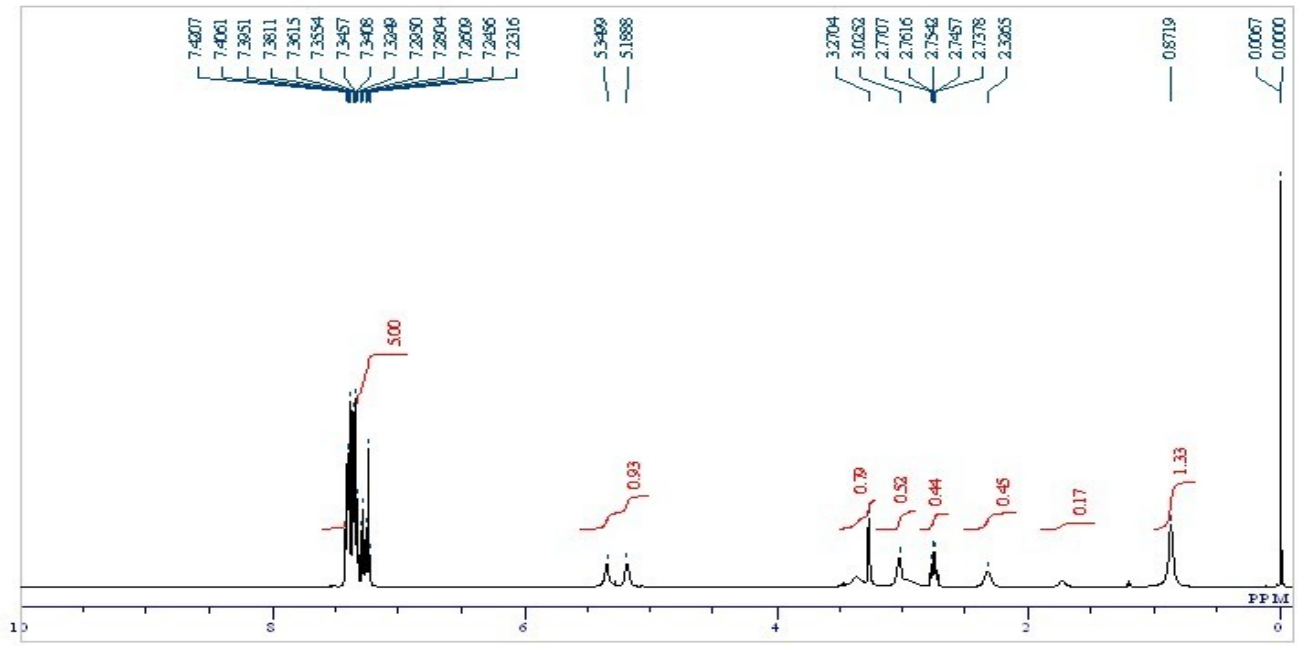
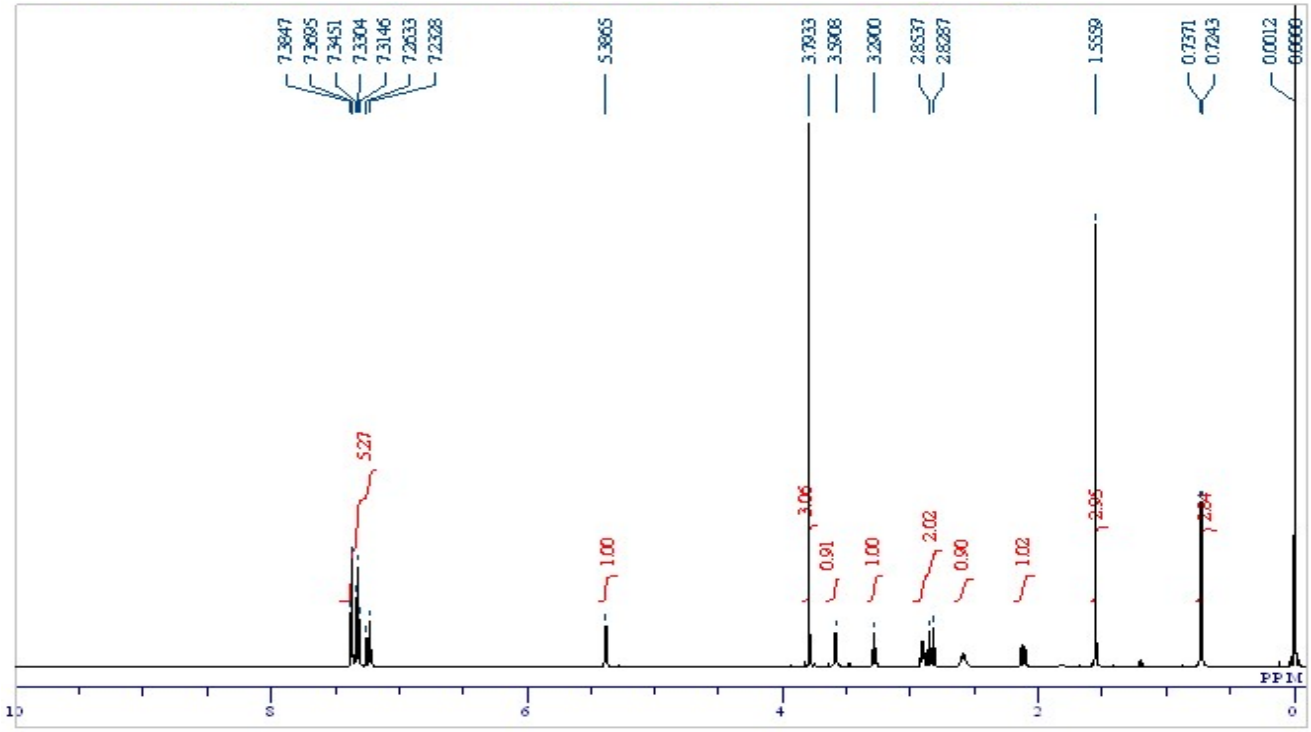
APPENDIX



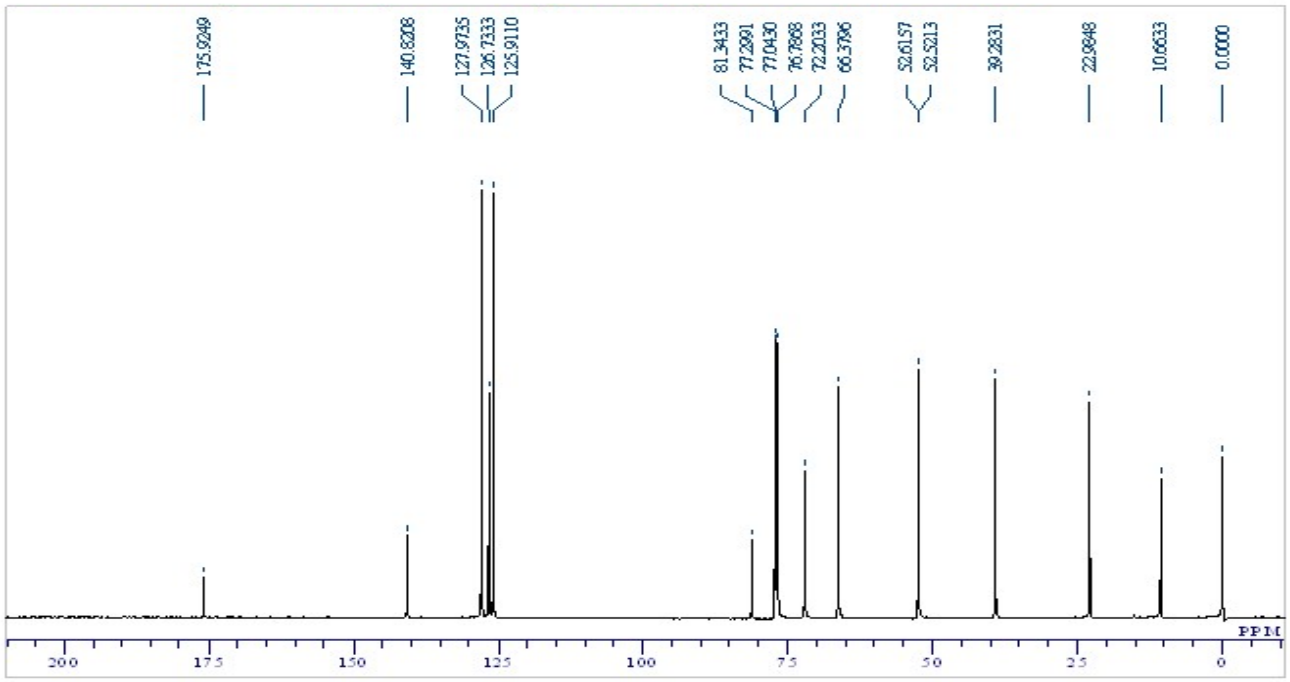
^{1}H-NMR of **127a** in $CDCl_3$ at 20°C



^{1}H-NMR of **127b** in $CDCl_3$ at 20°C



^{1}H-NMR of **131** in $CDCl_3$ at 20°C



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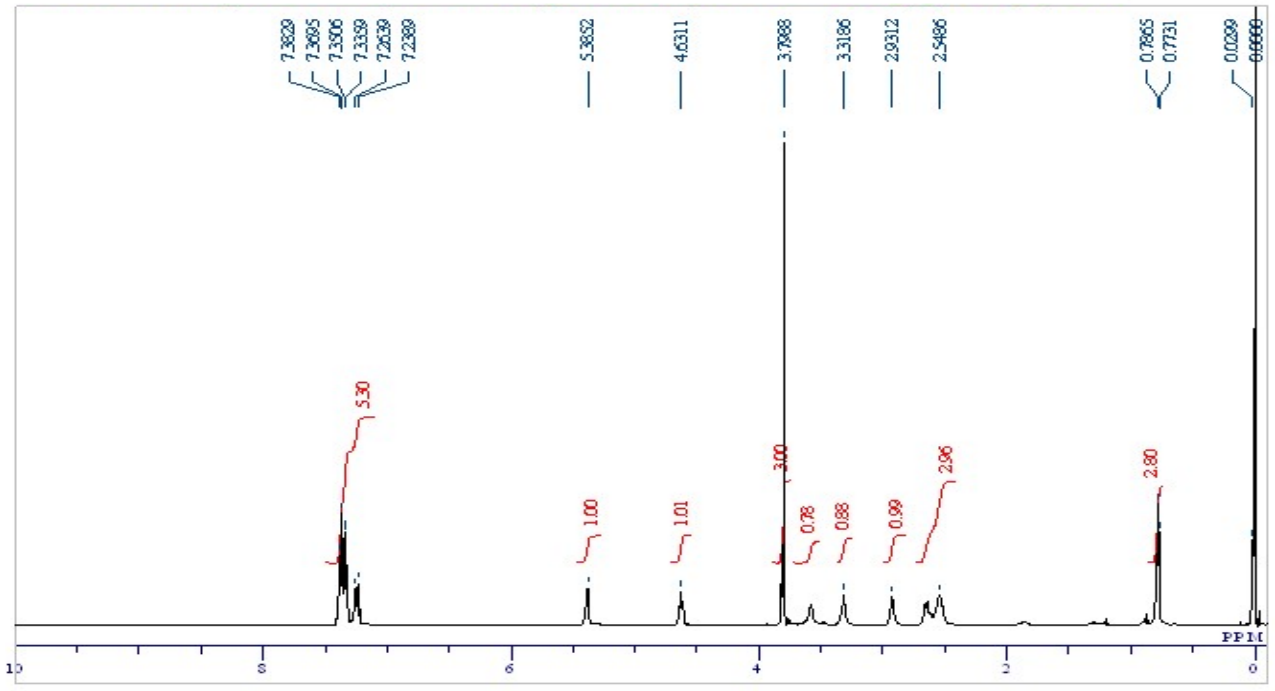
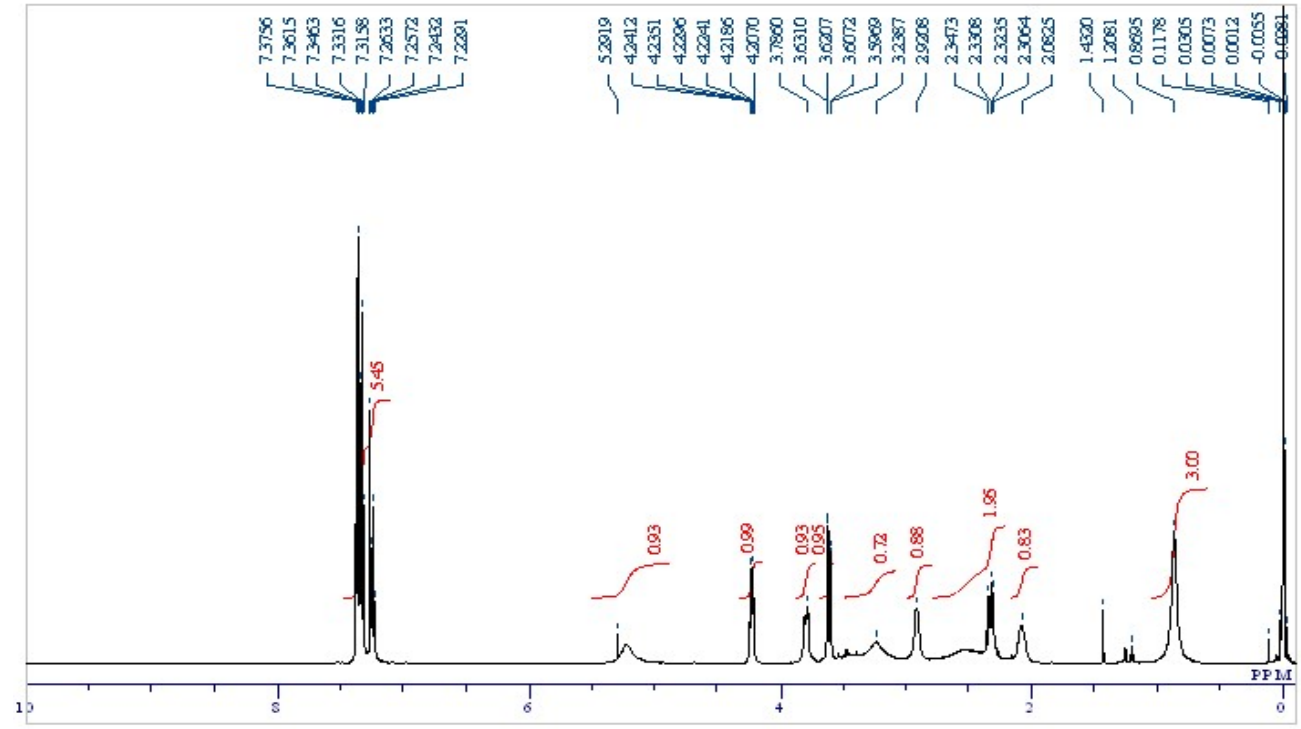


^{1}H-NMR of **128c** in $CDCl_3$ at 20°C



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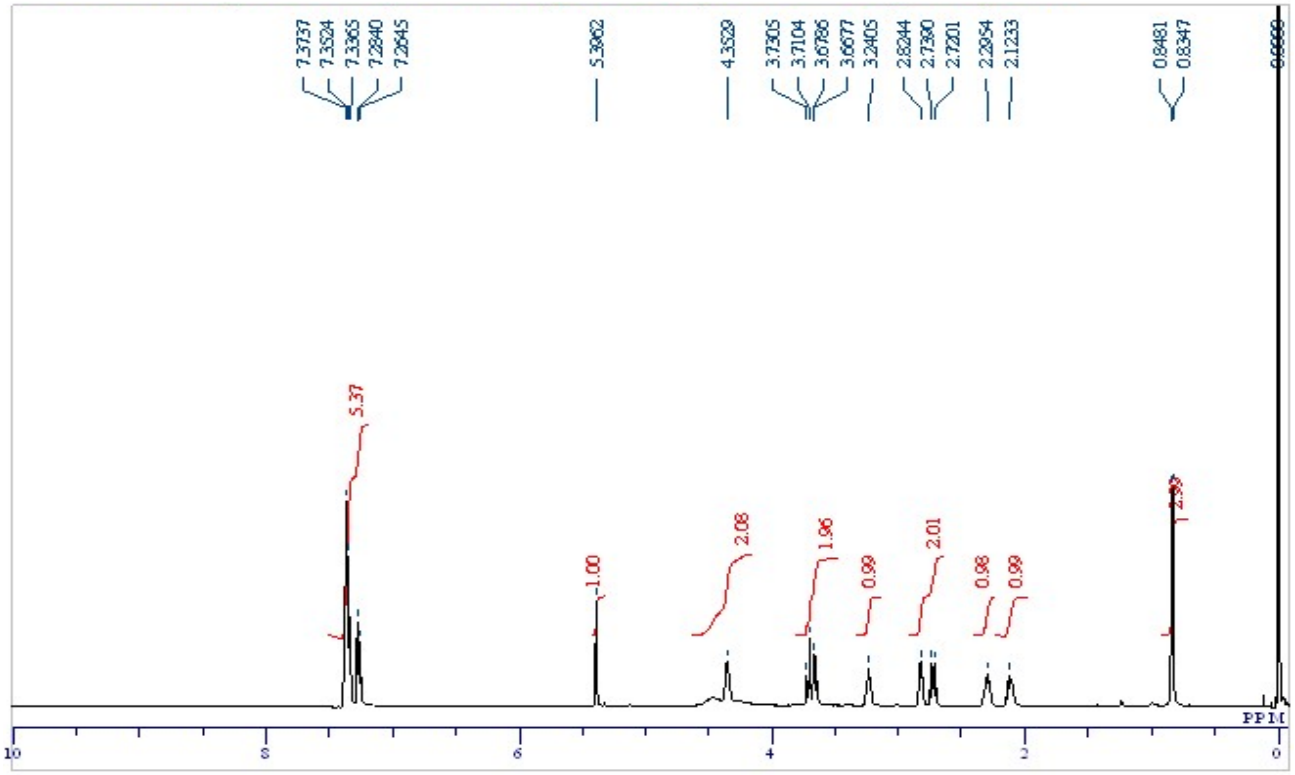
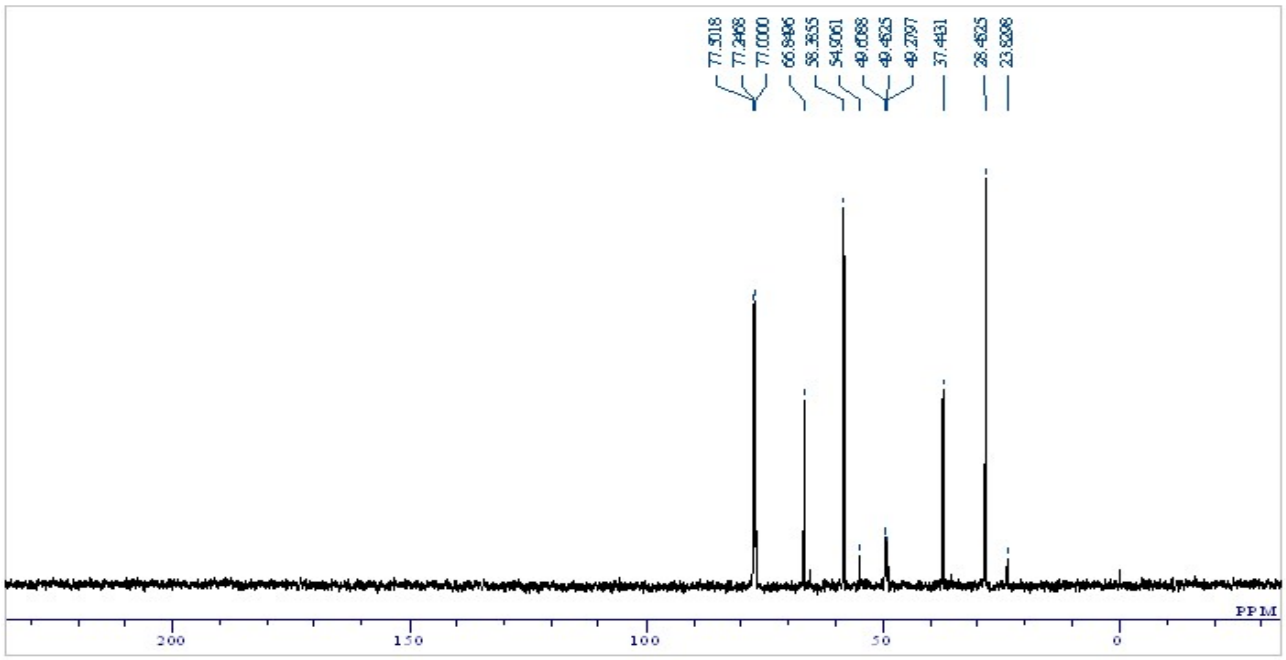


^{1}H-NMR of **127d** in $CDCl_3$ at 20°C



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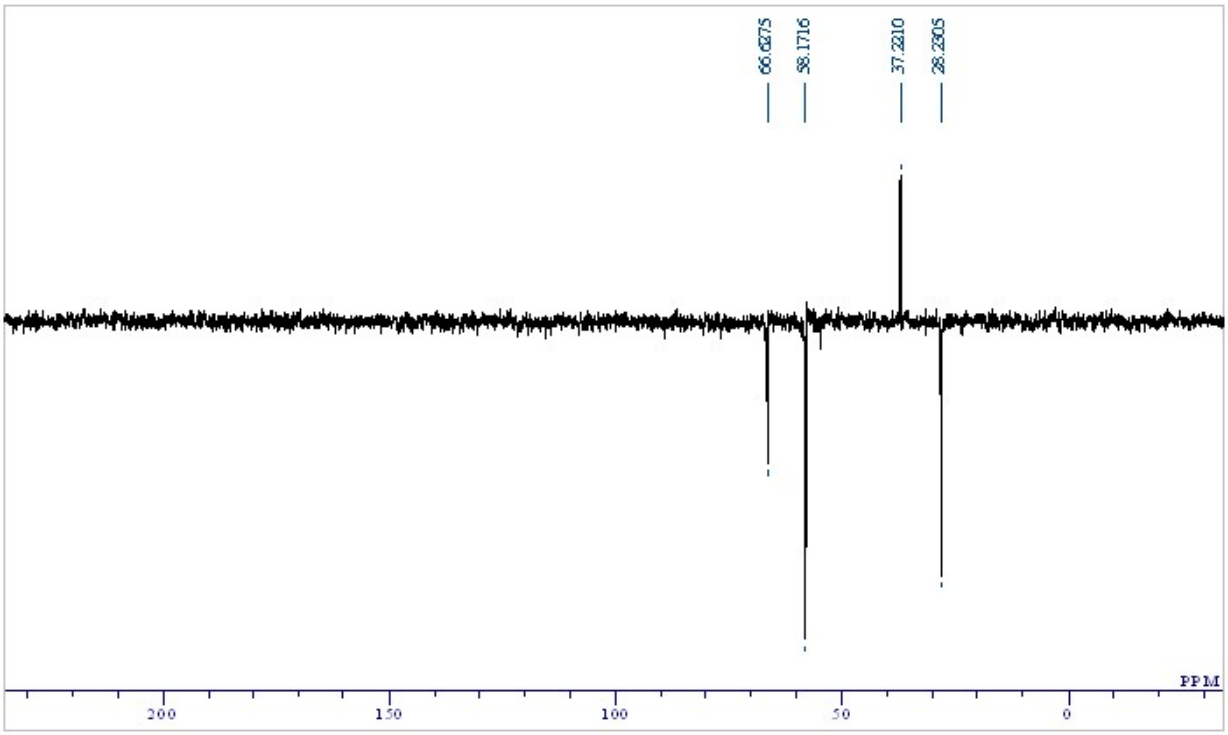
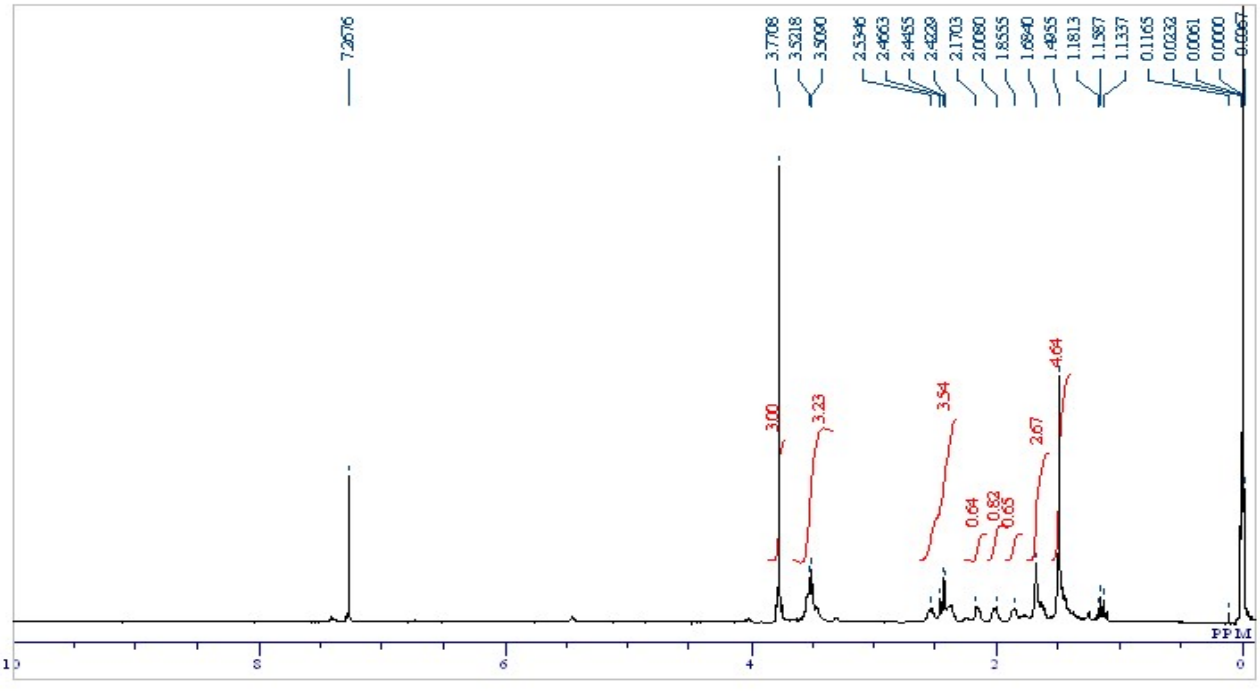
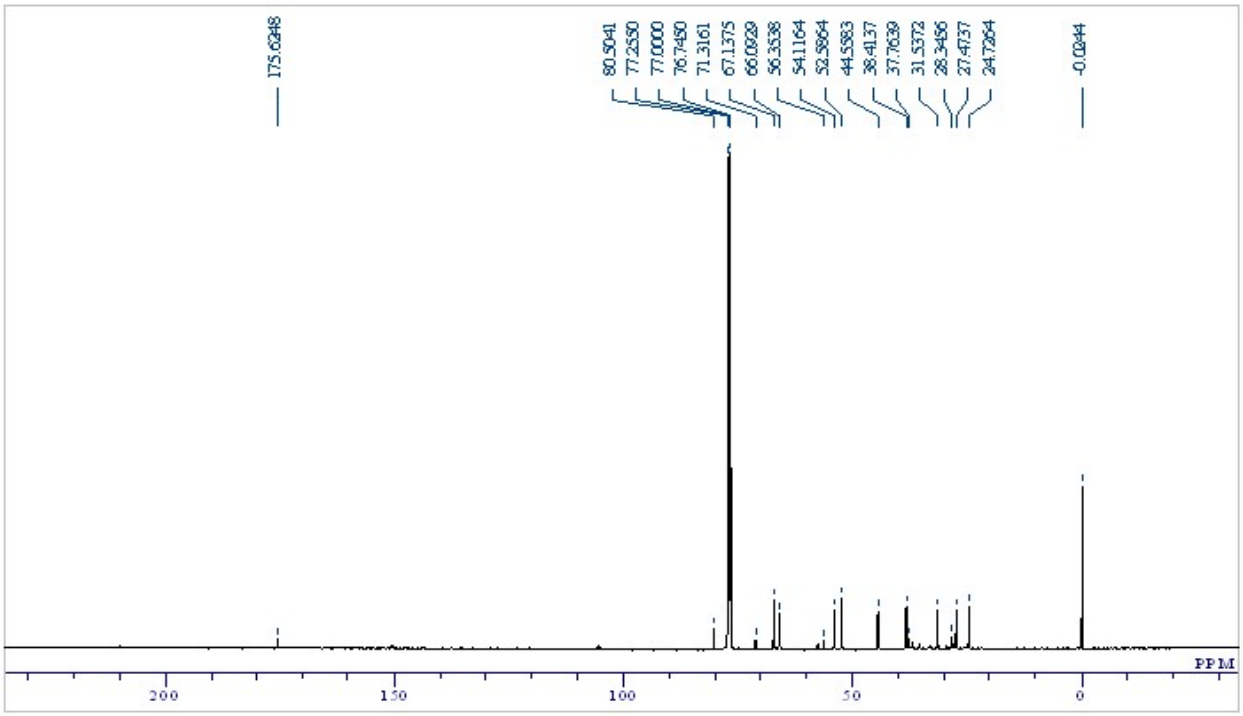


DEPT-NMR of **139** in $CDCl_3$ at 20°C



^{1}H-NMR of **155** in $CDCl_3$ at 20°C



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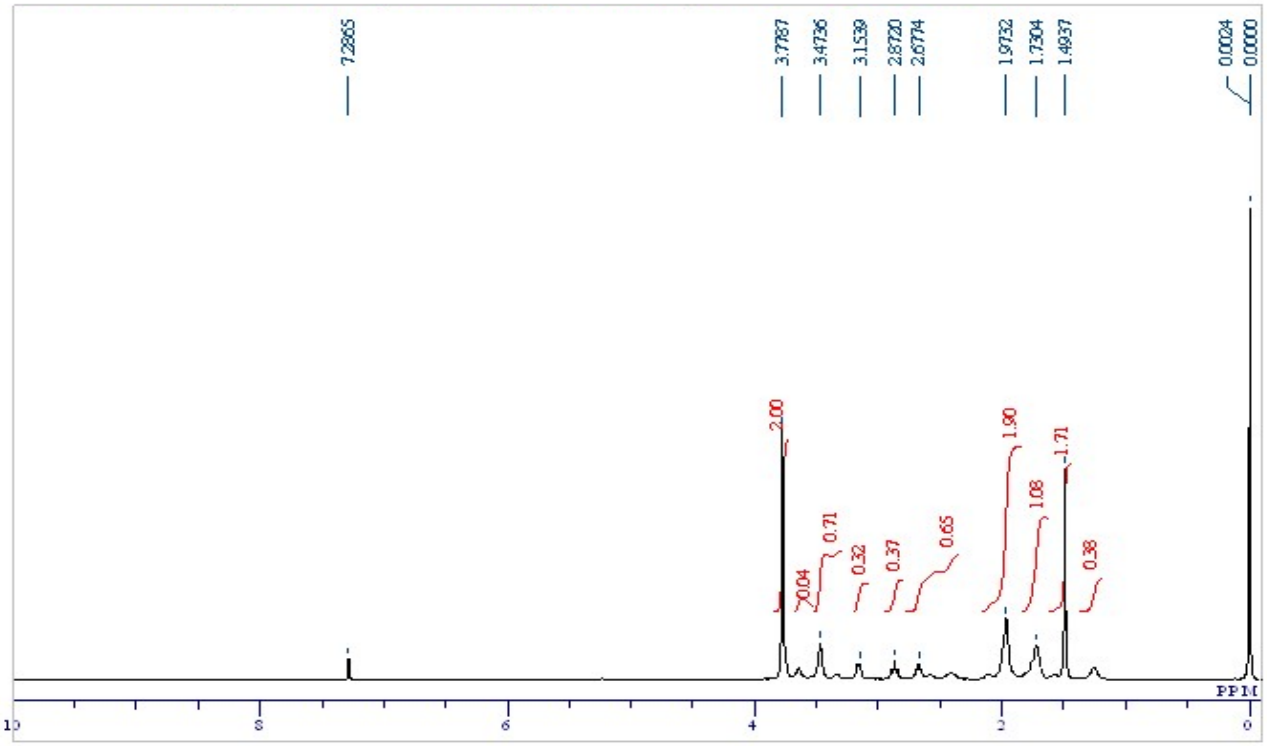

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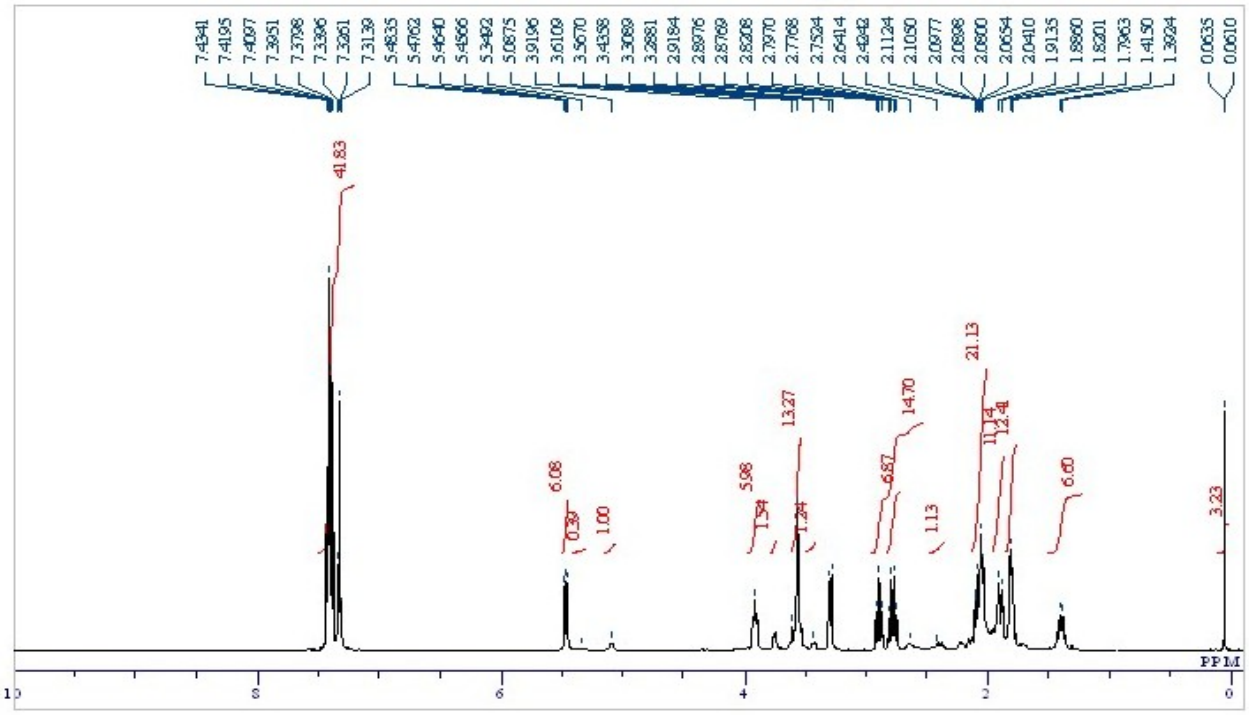

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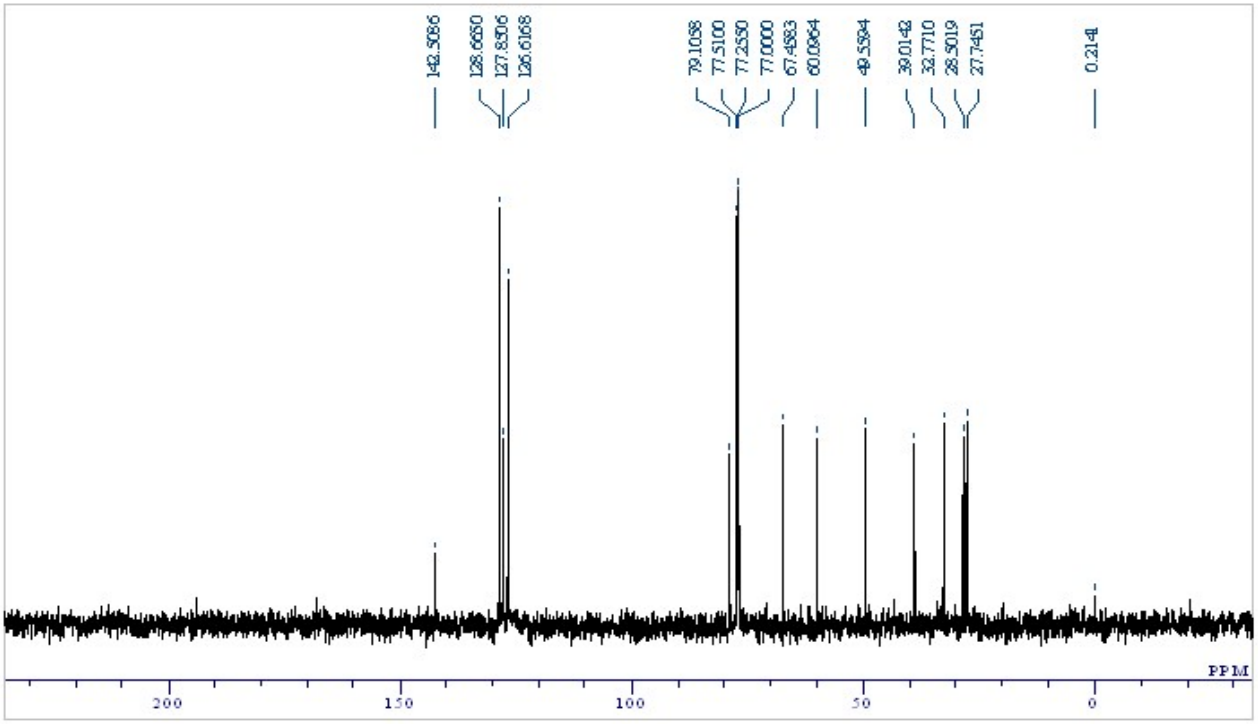

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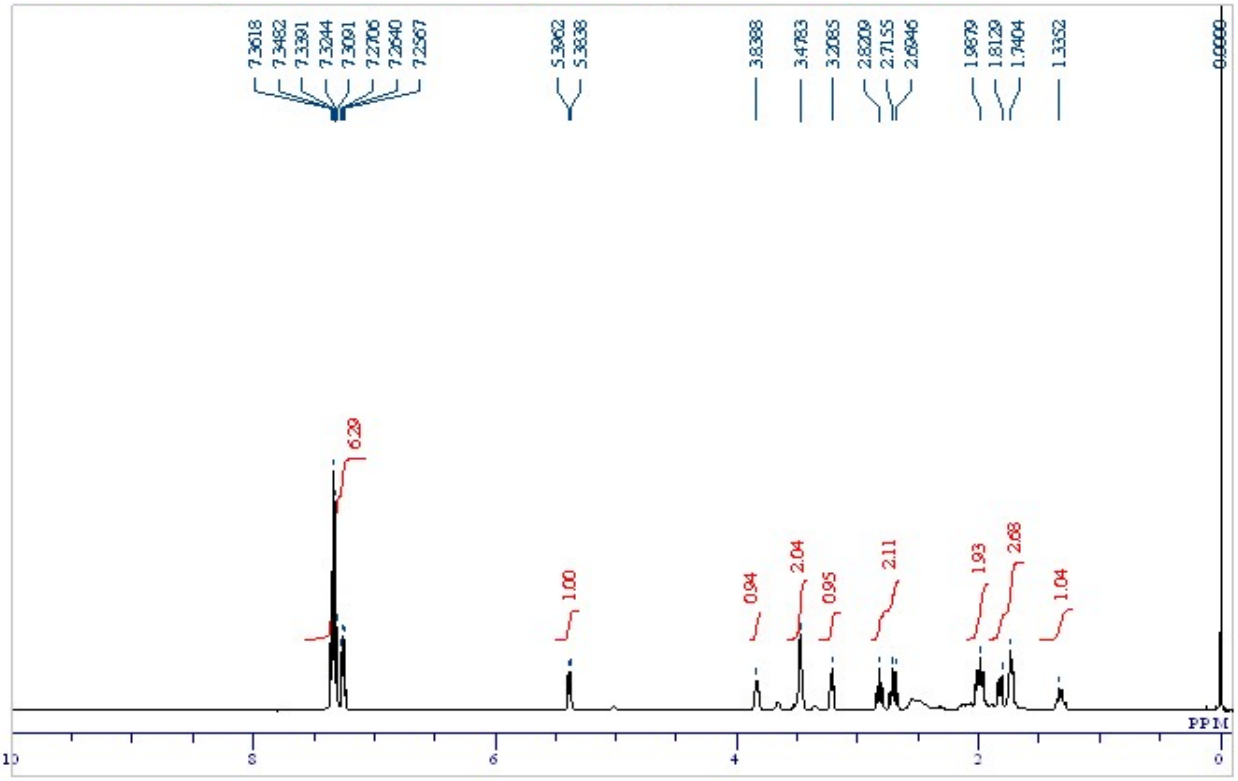

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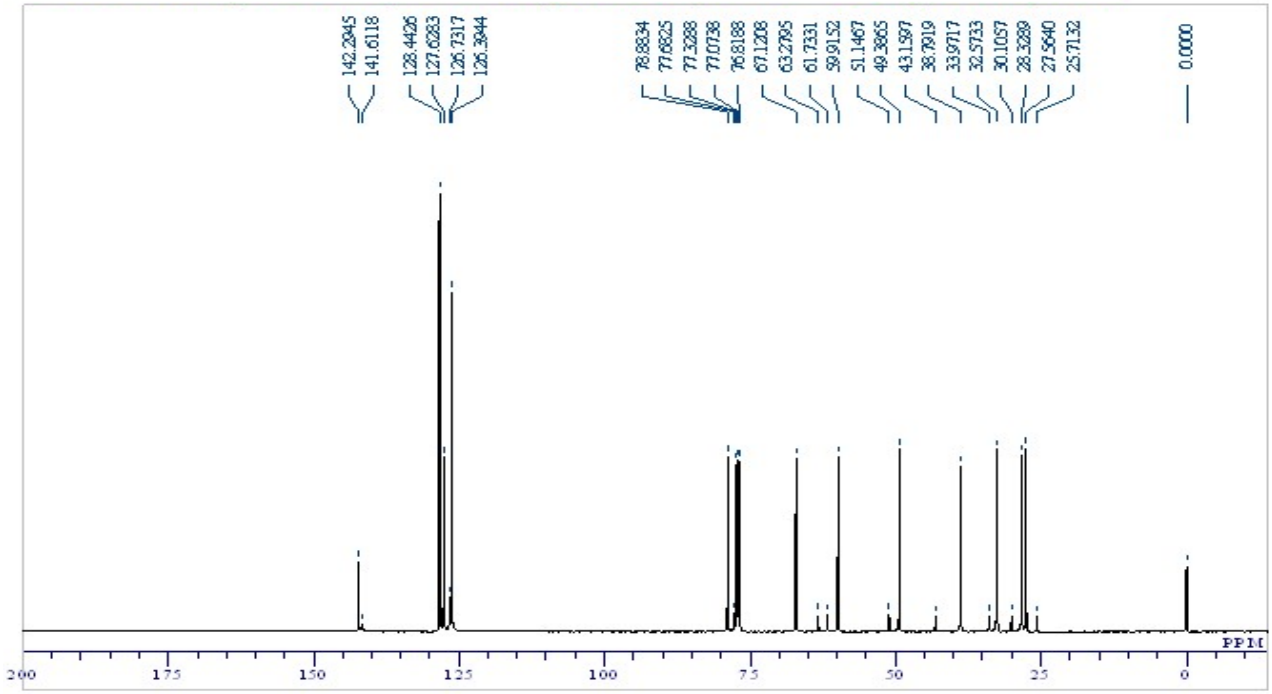

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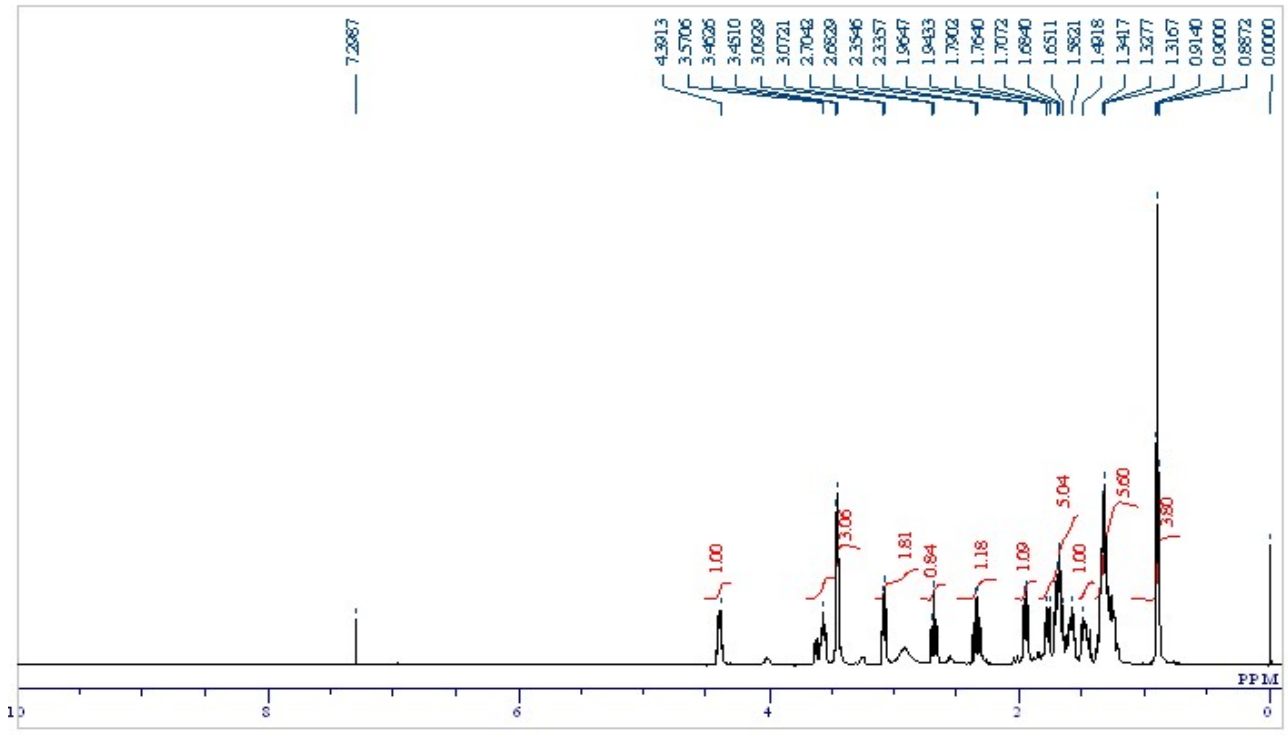
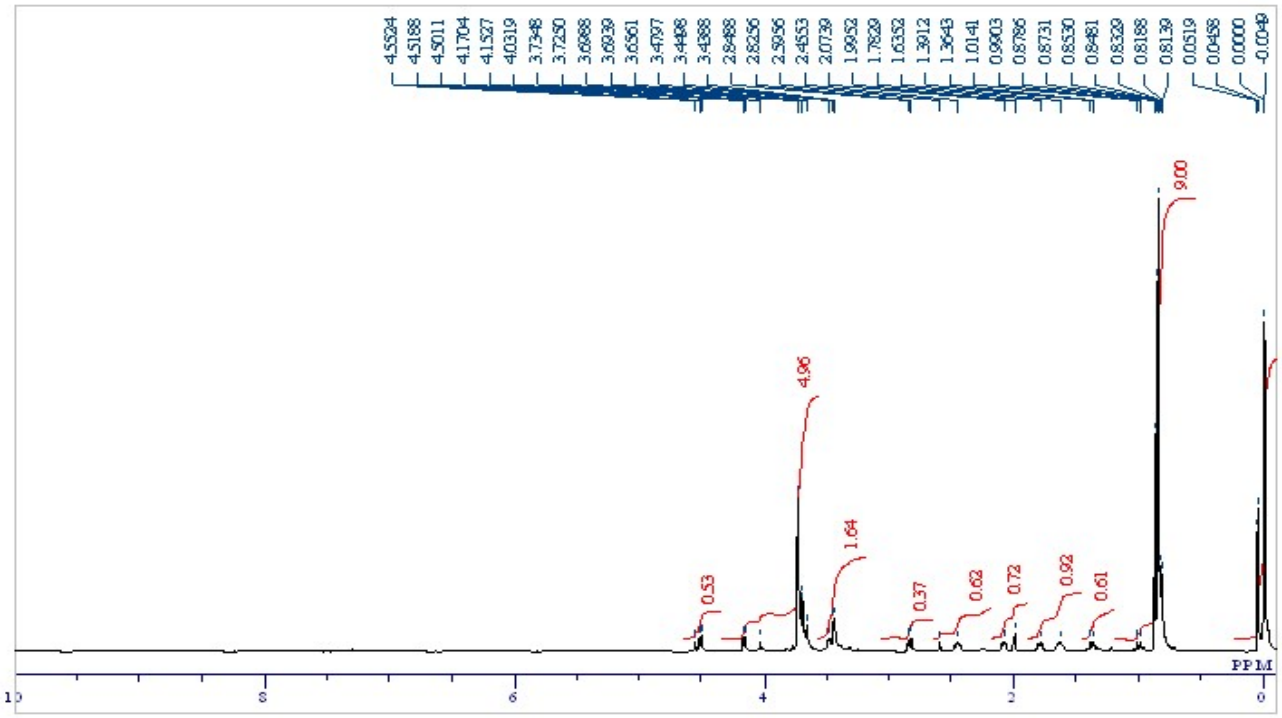


^{1}H-NMR of **142a** in $CDCl_3$ at 20°C



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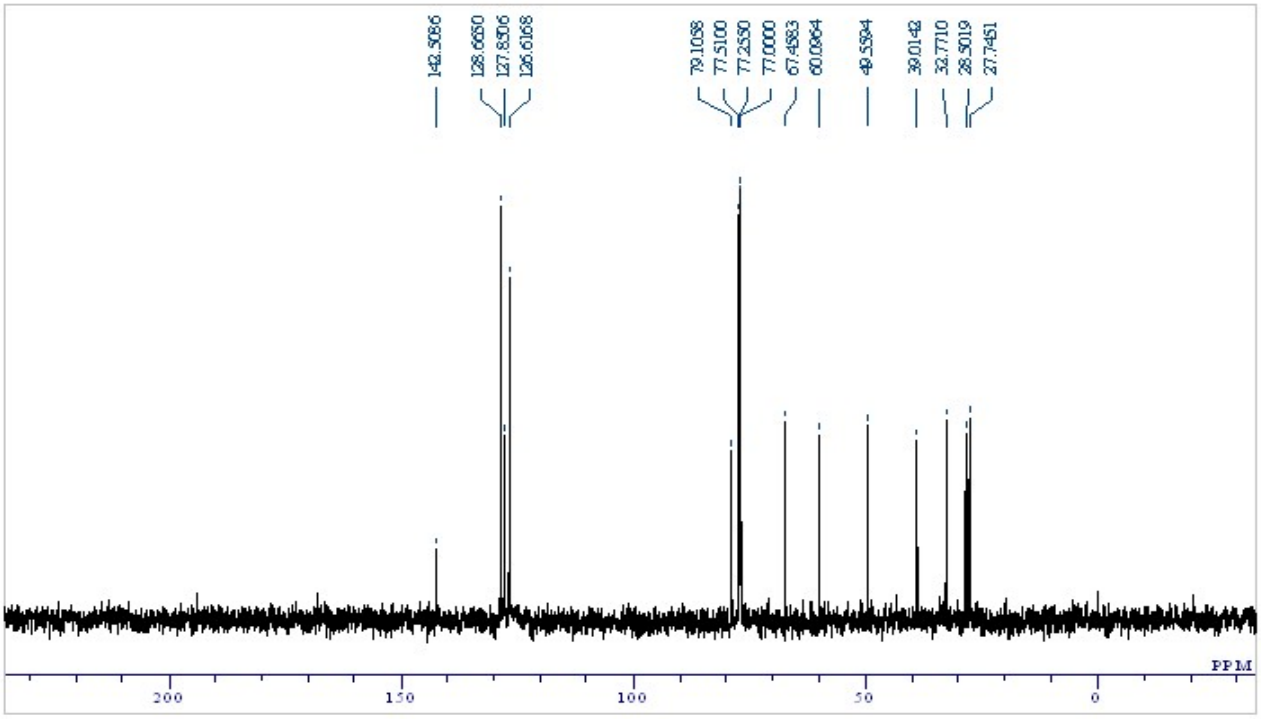

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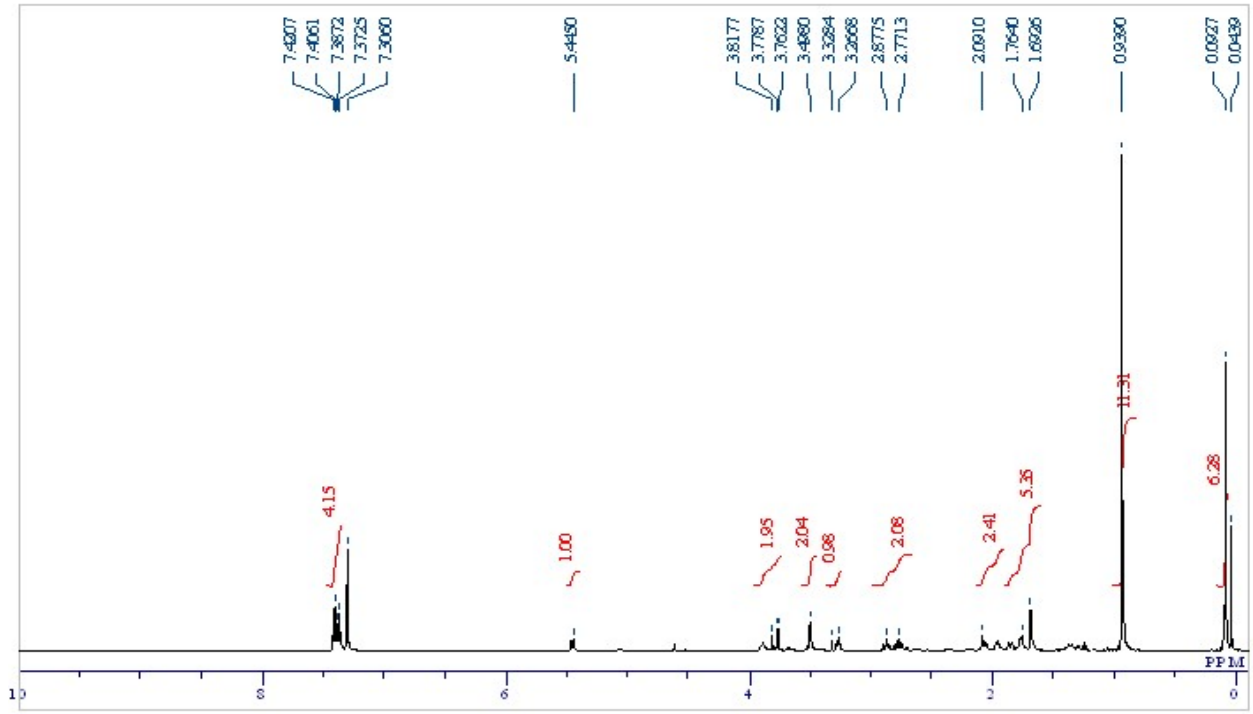

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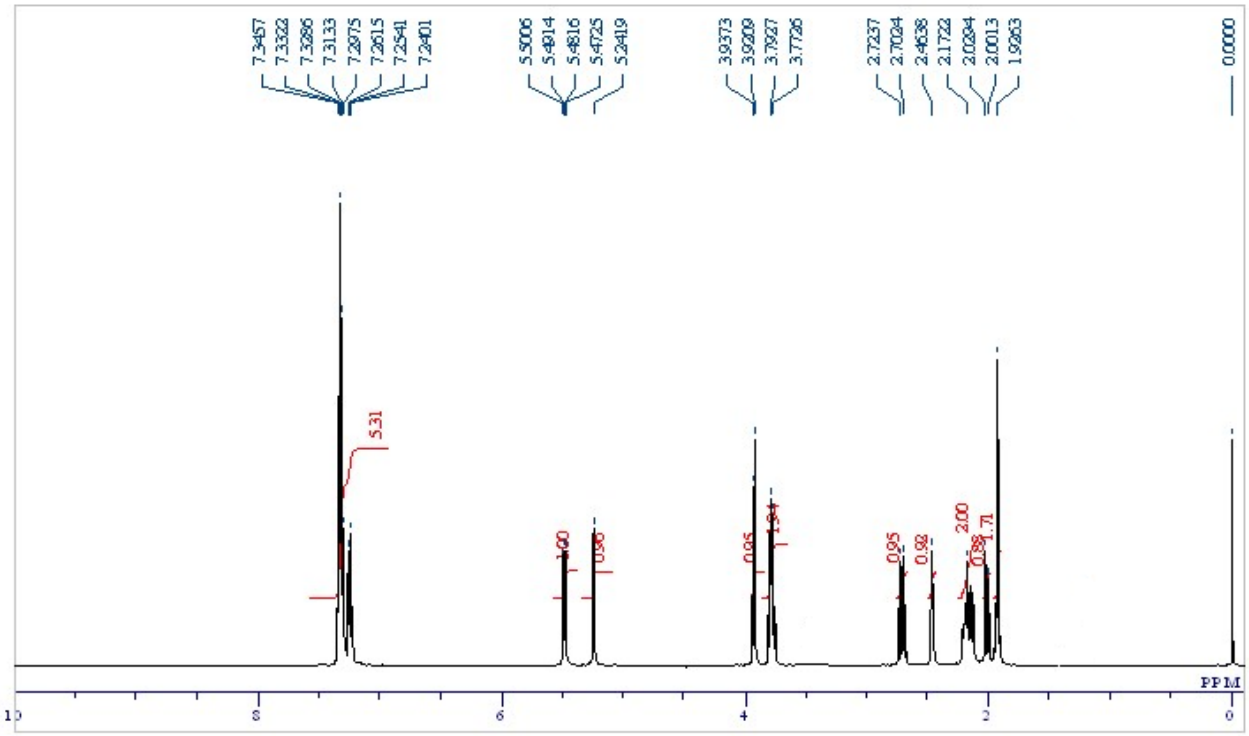
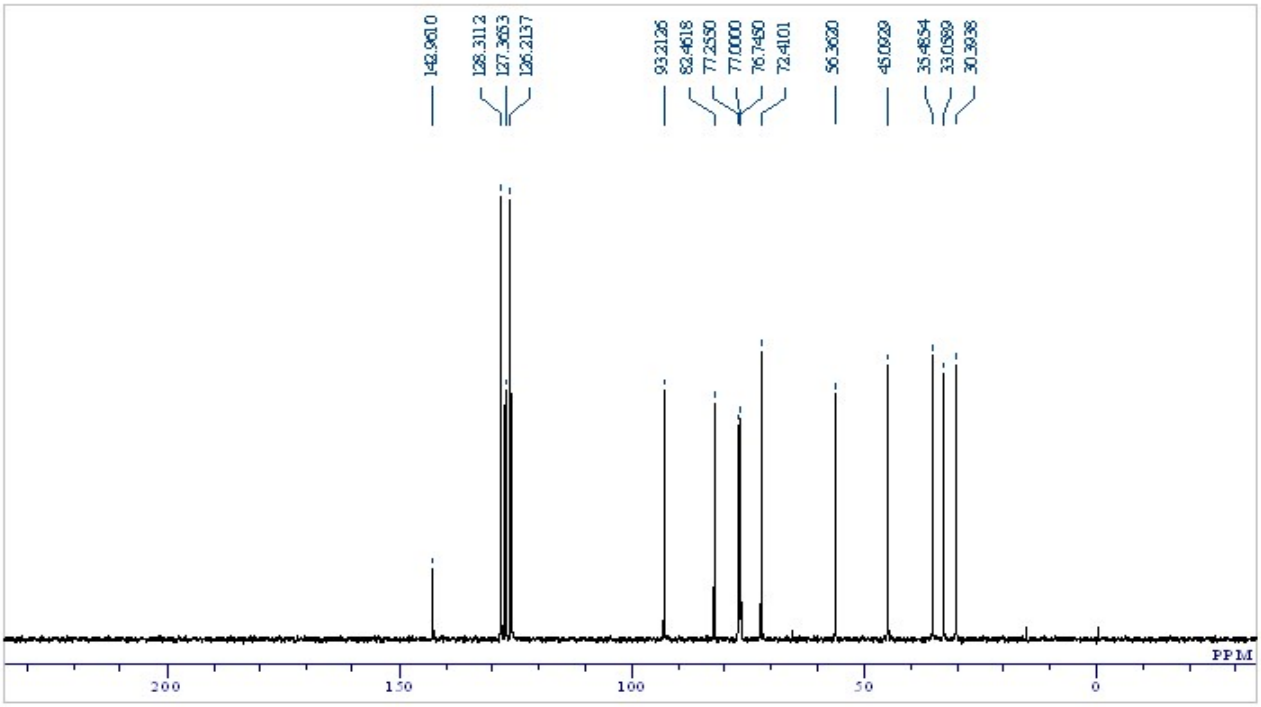
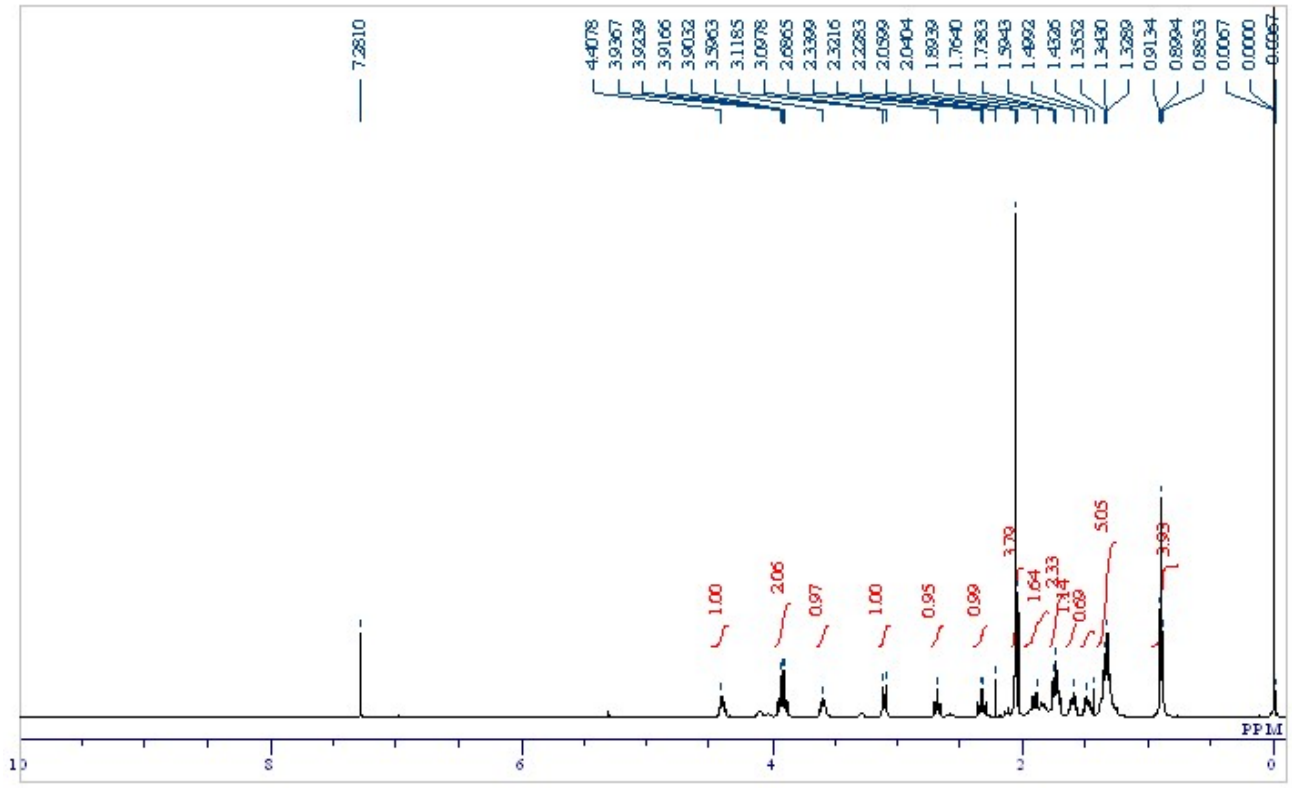


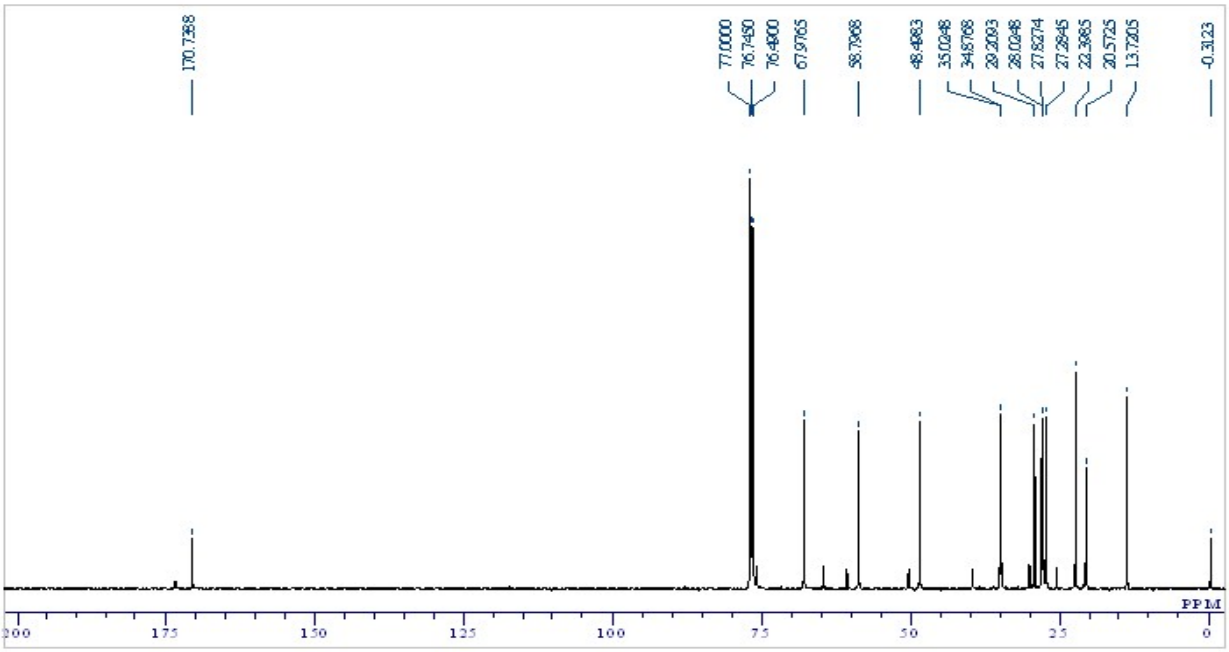
^{1}H-NMR of **218b** in $CDCl_3$ at 20°C



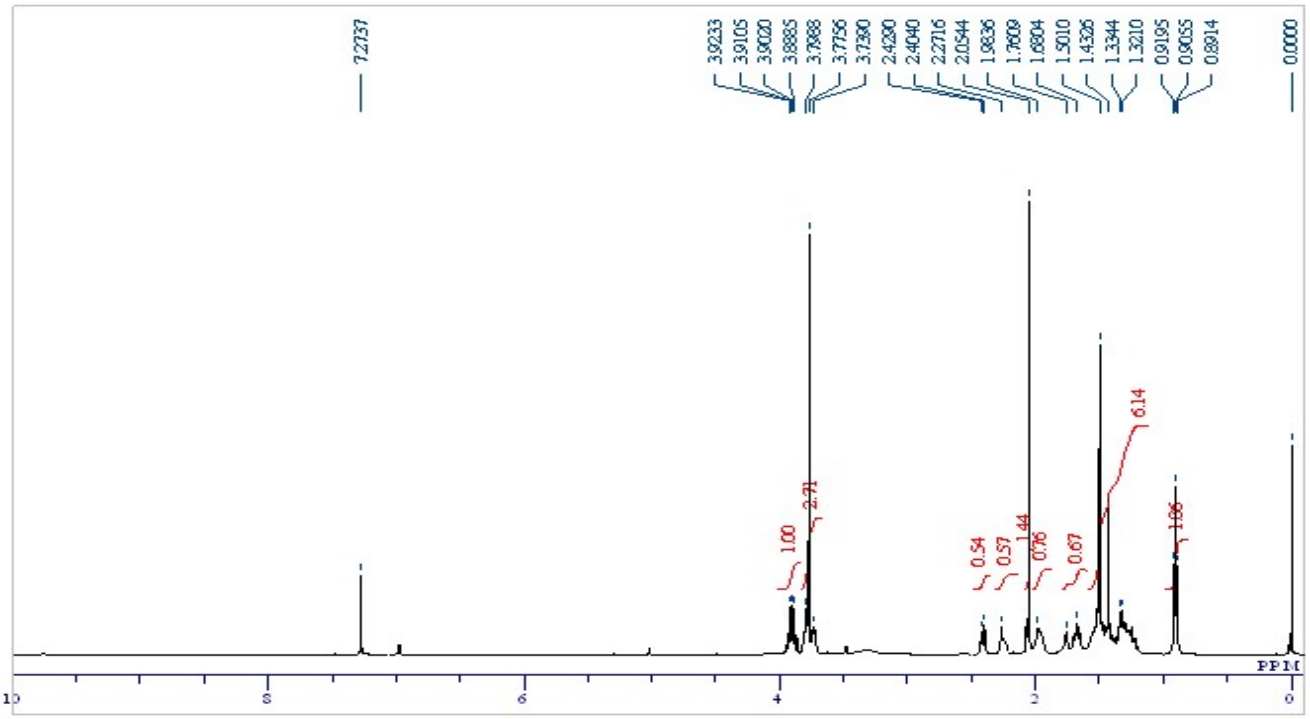
^{13}C-NMR of **218b** in $CDCl_3$ at 20°C



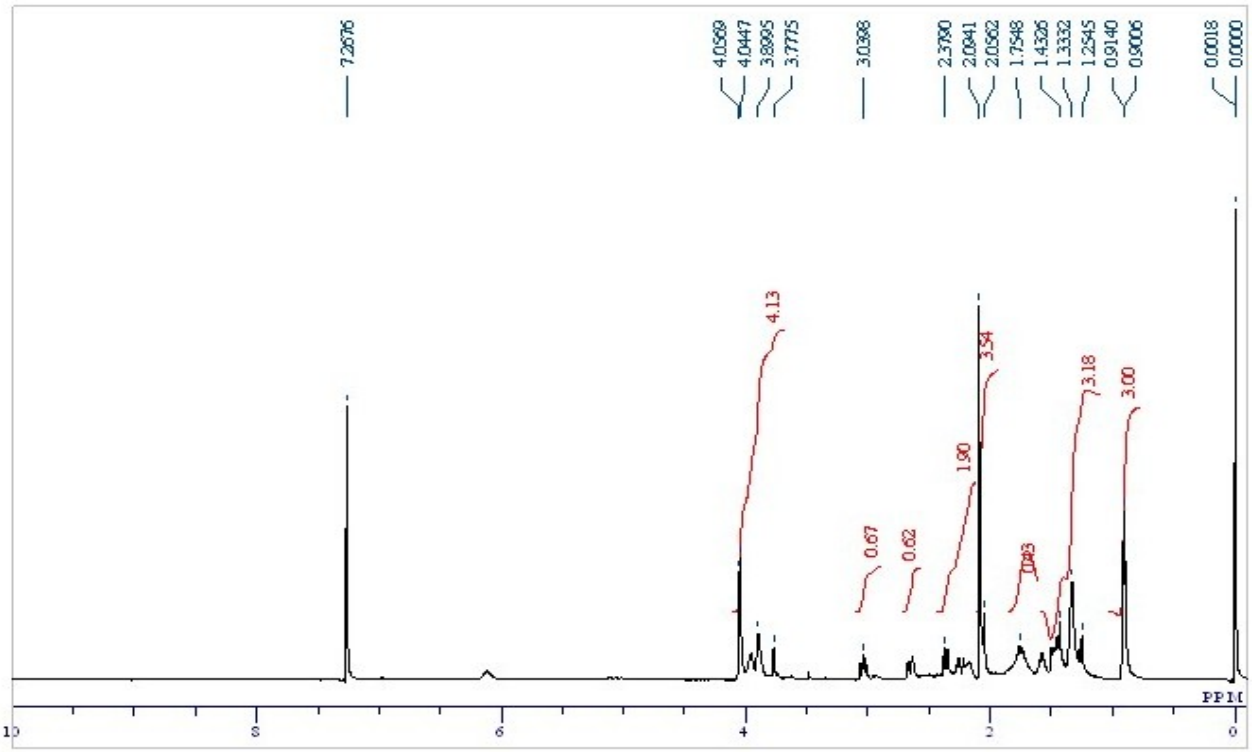
^{1}H-NMR of **168a** in $CDCl_3$ at 20°C



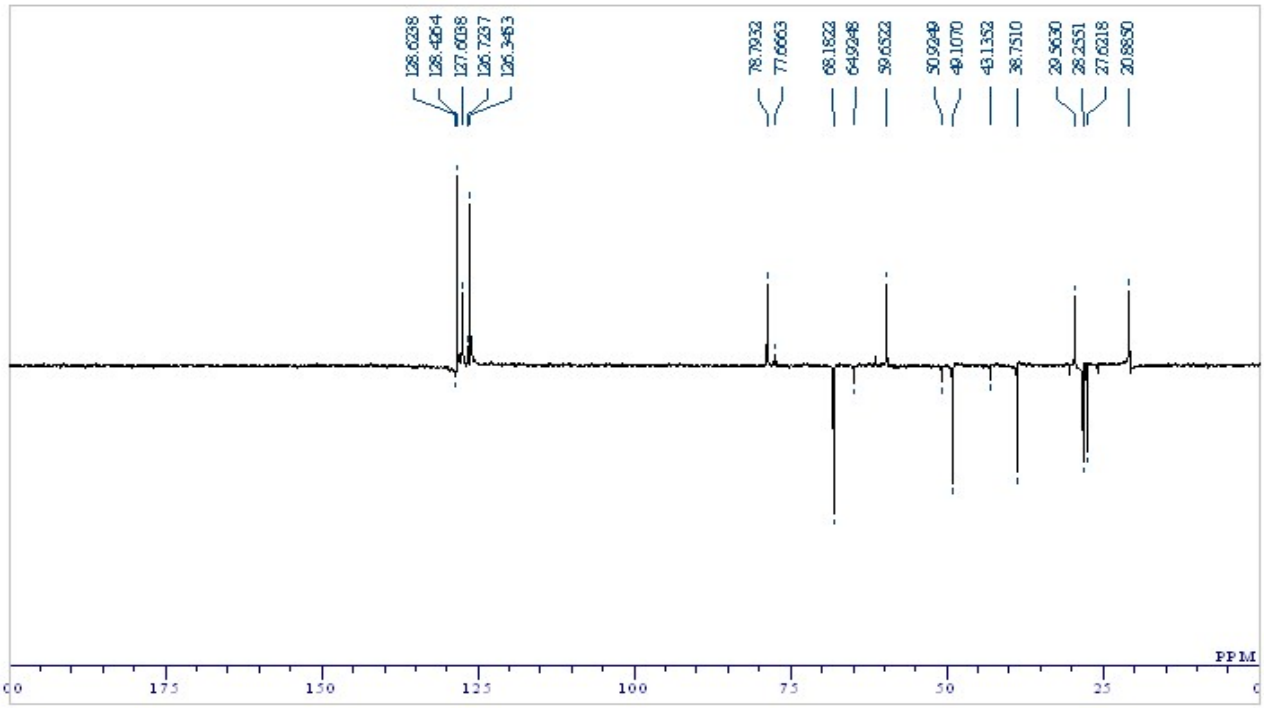
^{13}C-NMR of **168a** in $CDCl_3$ at 20°C



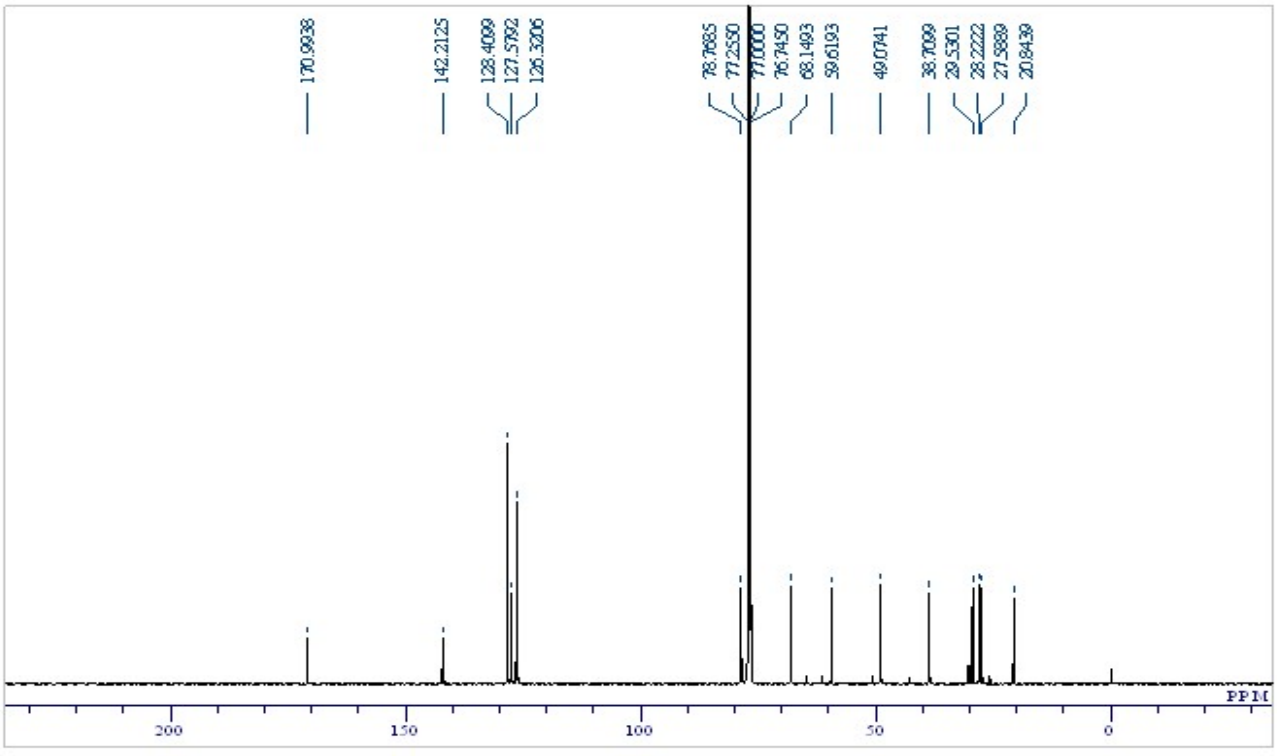
^{1}H-NMR of **176** in $CDCl_3$ at 20°C



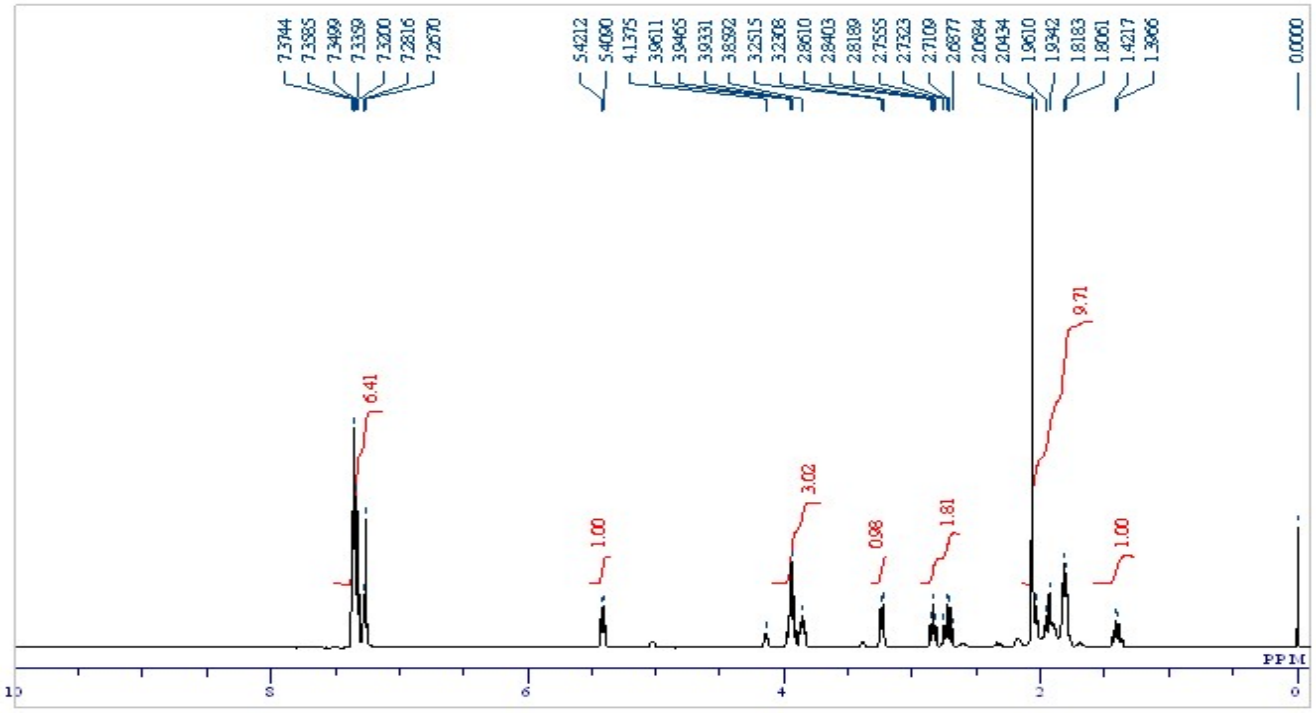
^{1}H-NMR of **170a** in $CDCl_3$ at 20°C



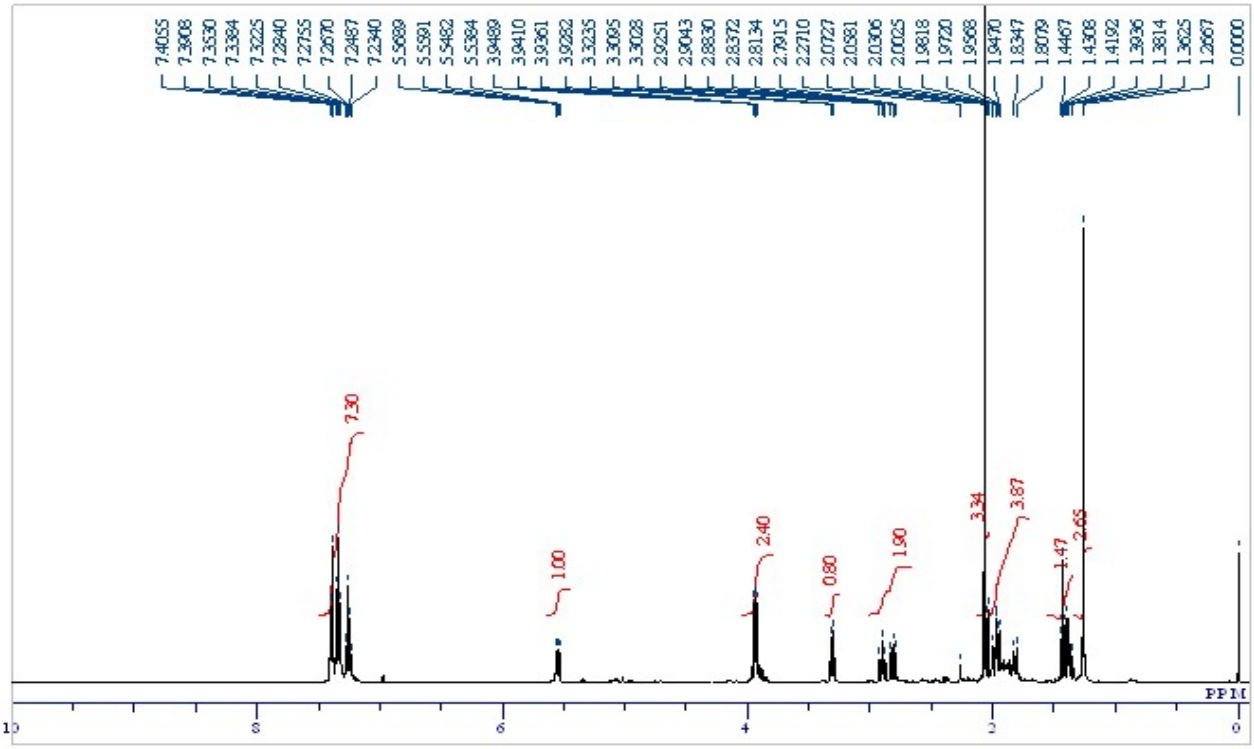
DEPT-NMR of **168b** in $CDCl_3$ at 20°C



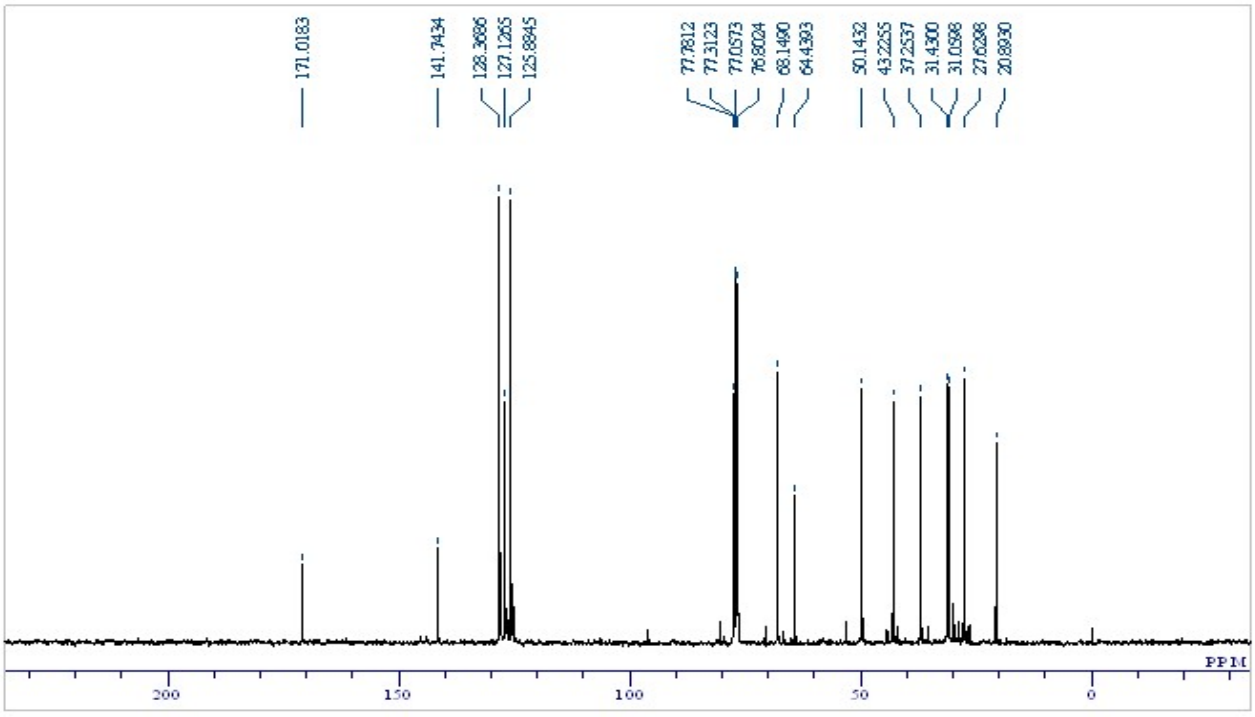
^{13}C-NMR of **168b** in $CDCl_3$ at 20°C



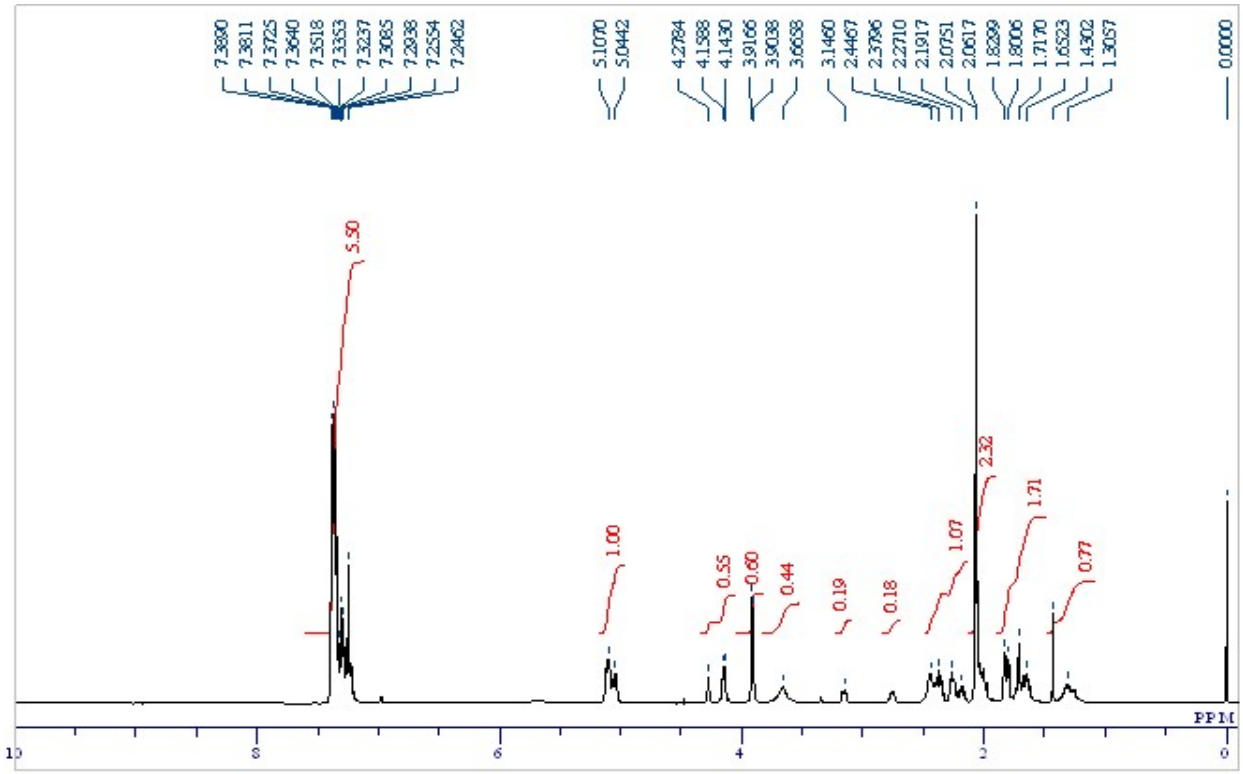
^{1}H-NMR of **168b** in $CDCl_3$ at 20°C



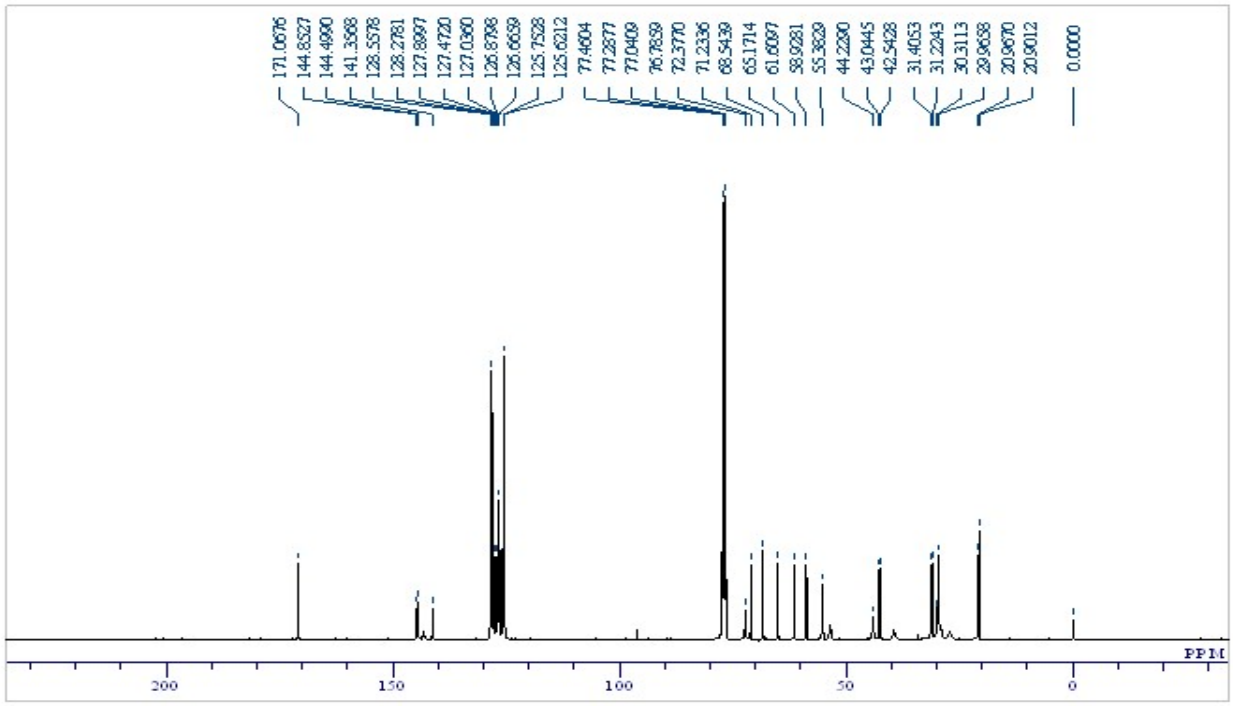
^{1}H-NMR of **172** in $CDCl_3$ at 20°C



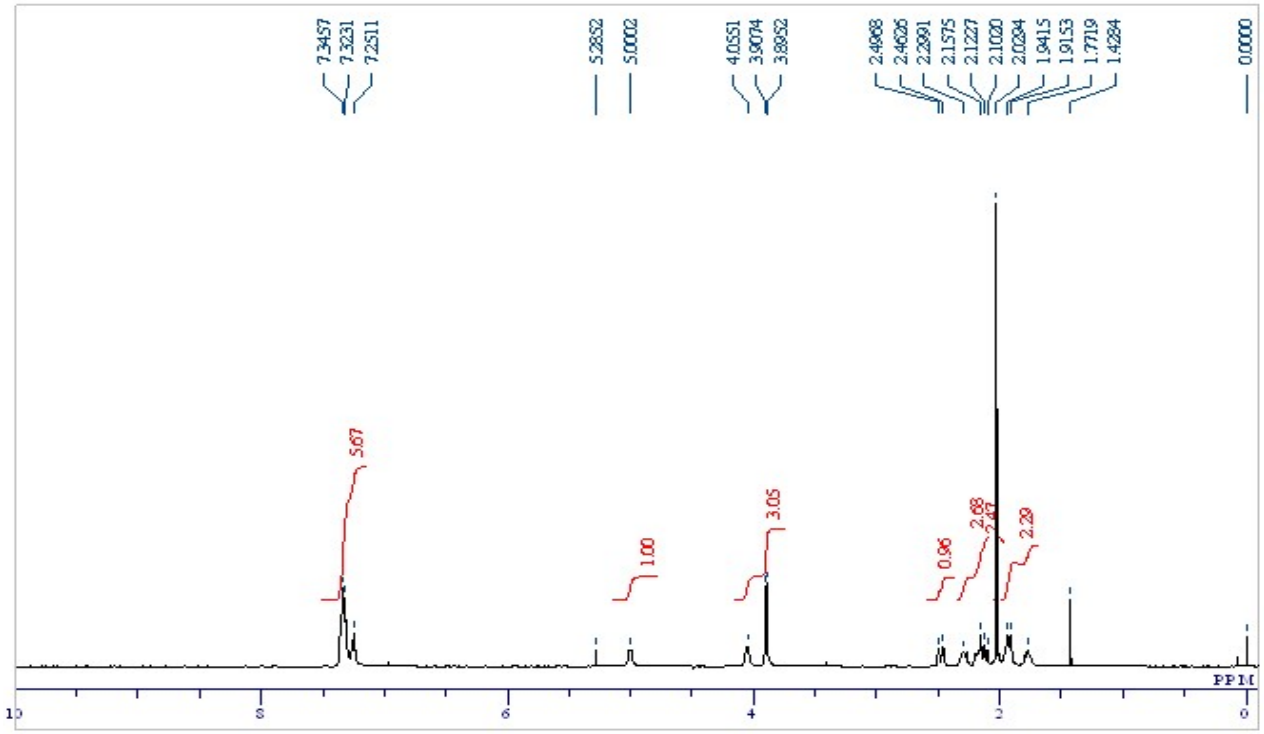
^{13}C-NMR of **172** in $CDCl_3$ at 20°C



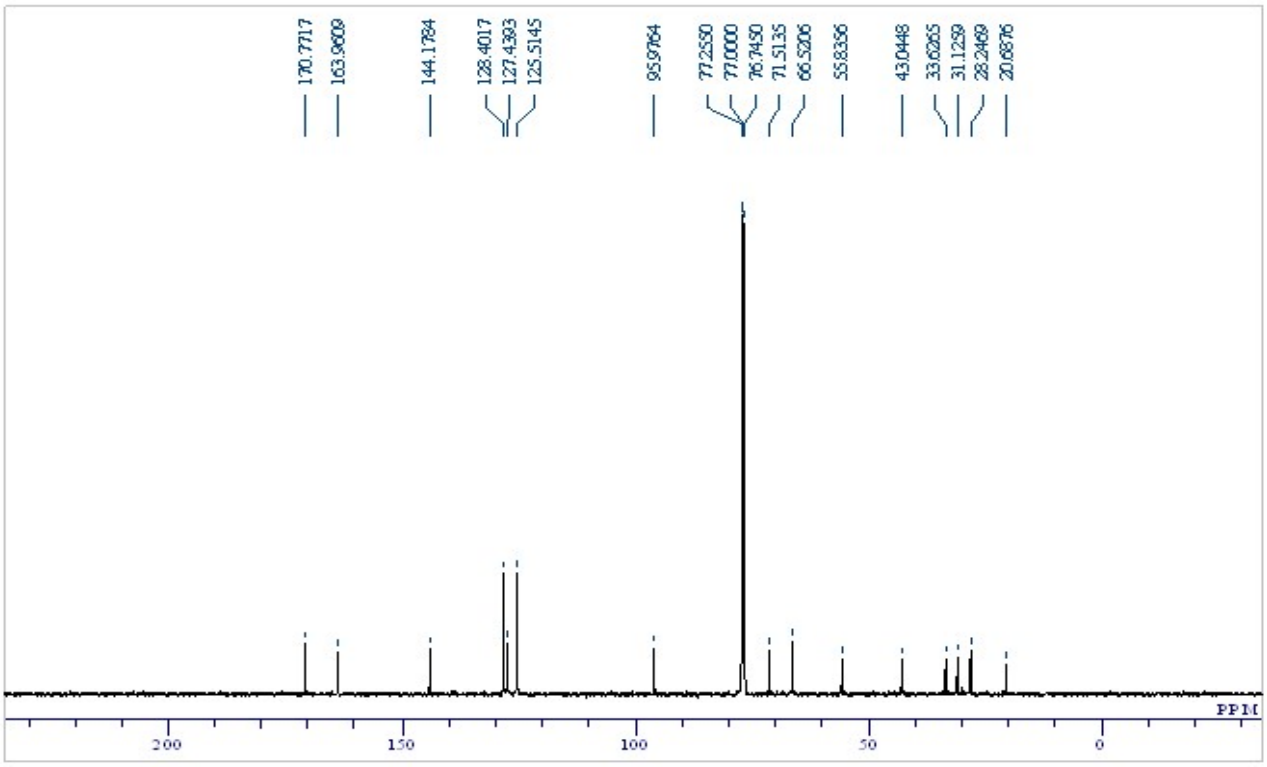
^{1}H-NMR of **173** in $CDCl_3$ at 20°C



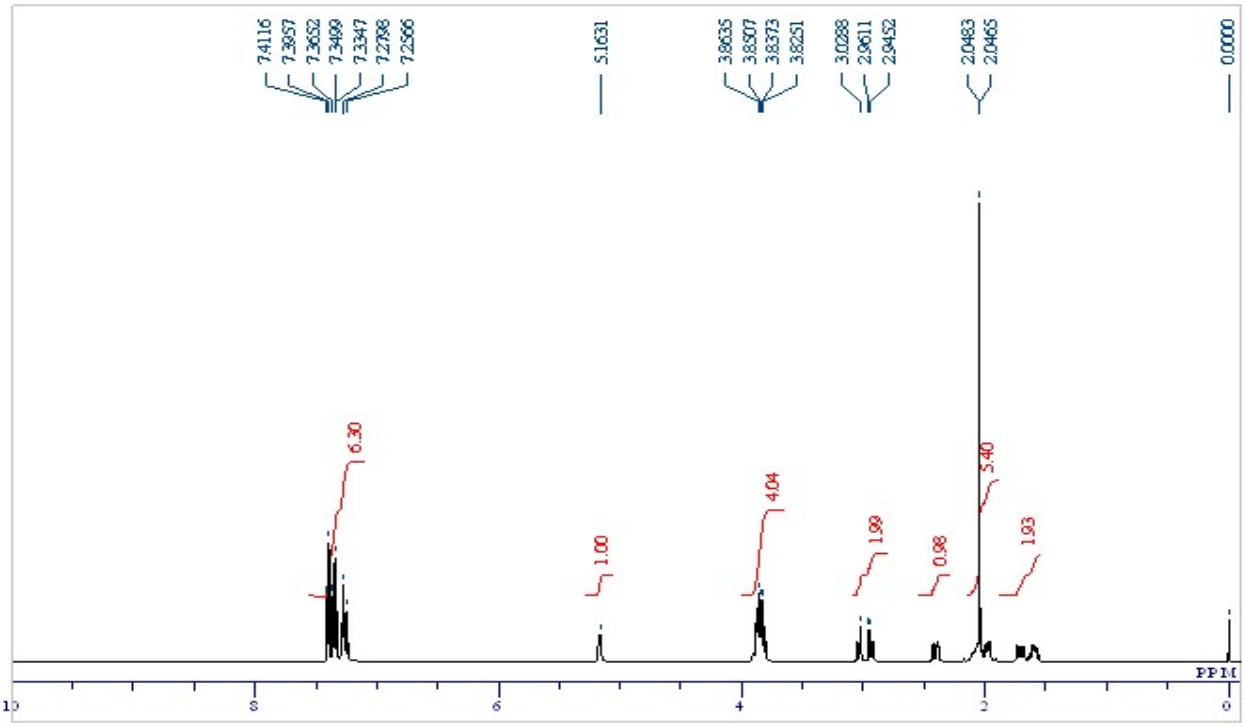
^{13}C-NMR of **173** in $CDCl_3$ at 20°C



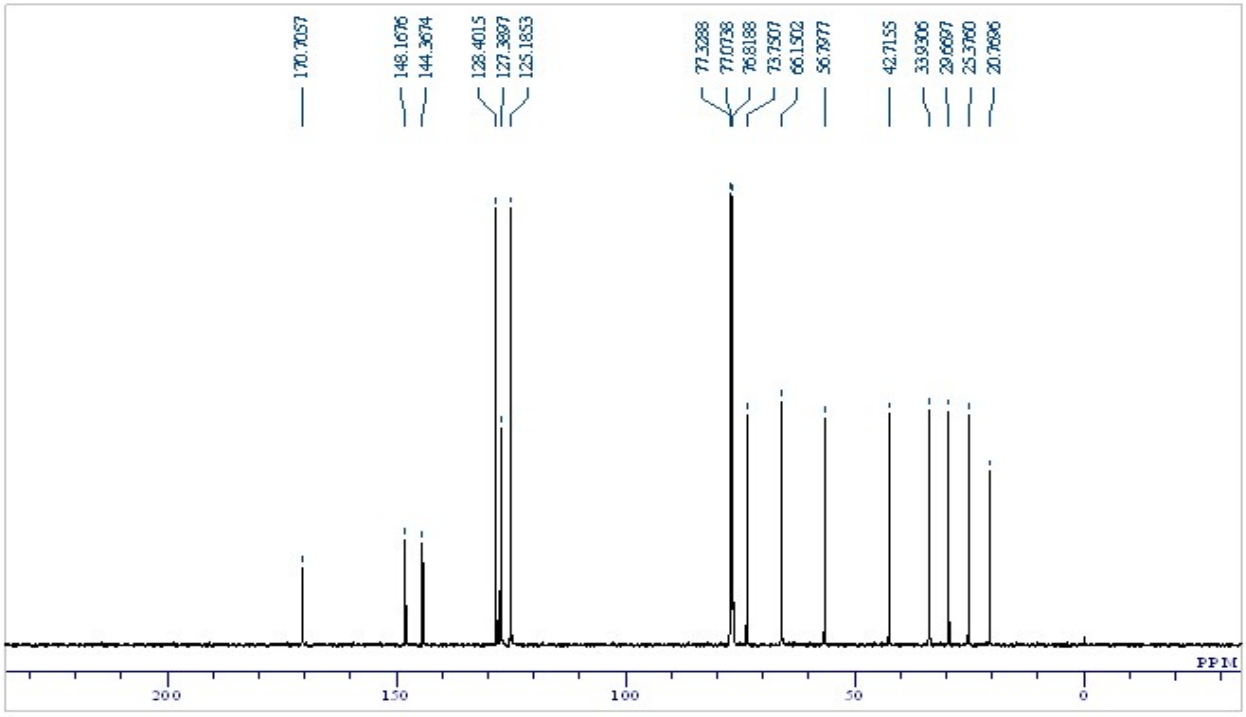
^{1}H-NMR of **171b** in $CDCl_3$ at 20°C



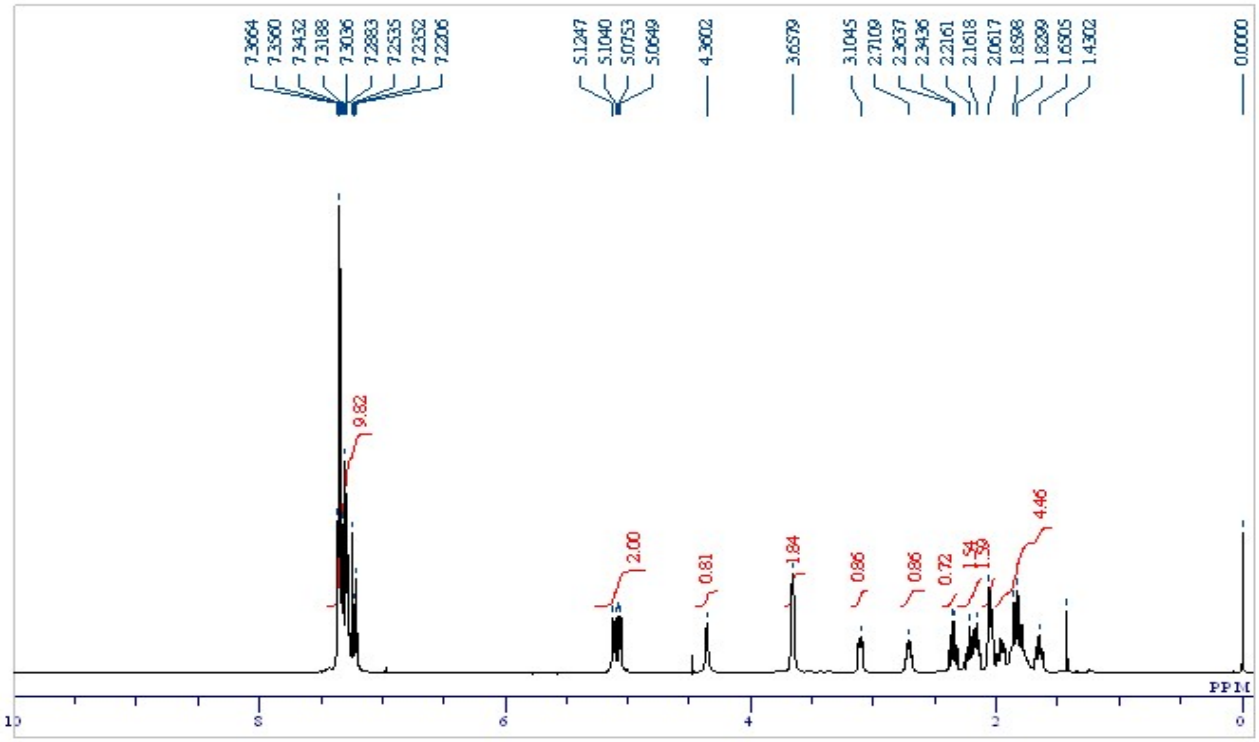
^{13}C-NMR of **171b** in $CDCl_3$ at 20°C



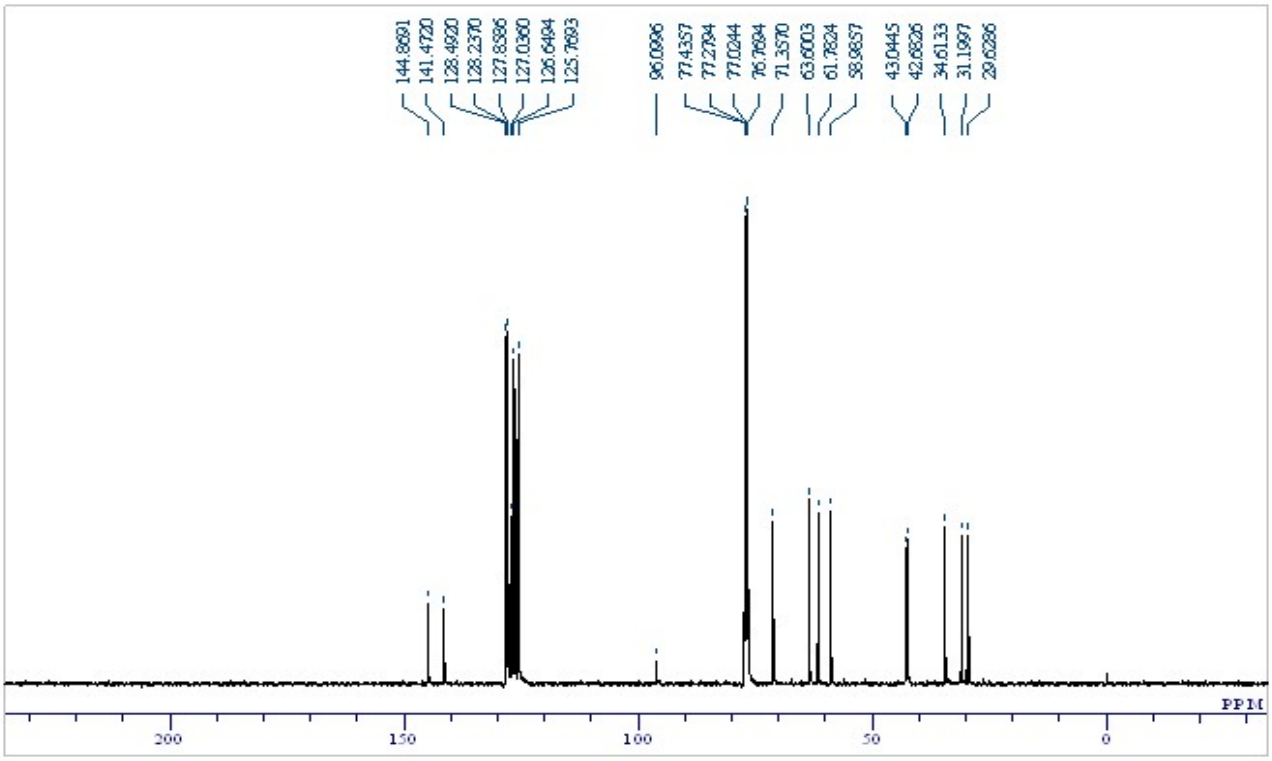
^{1}H-NMR of **170b** in $CDCl_3$ at 20°C



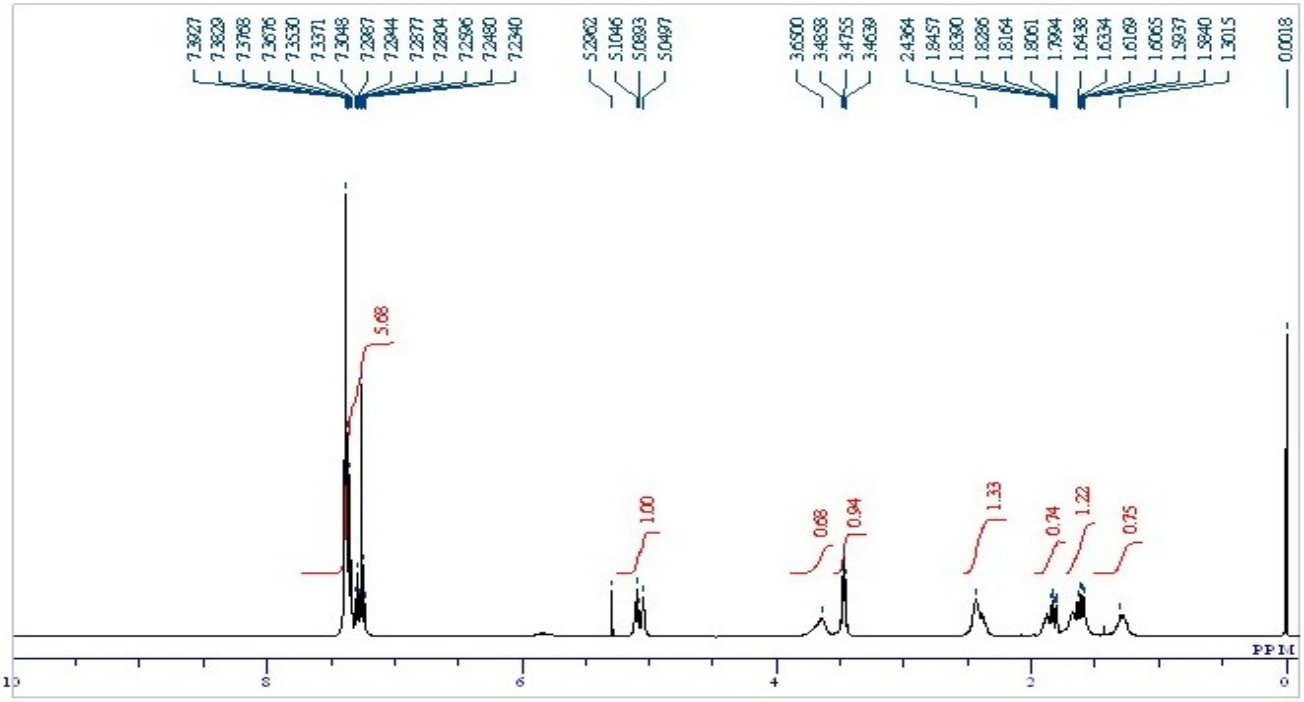
^{13}C-NMR of **170b** in $CDCl_3$ at 20°C



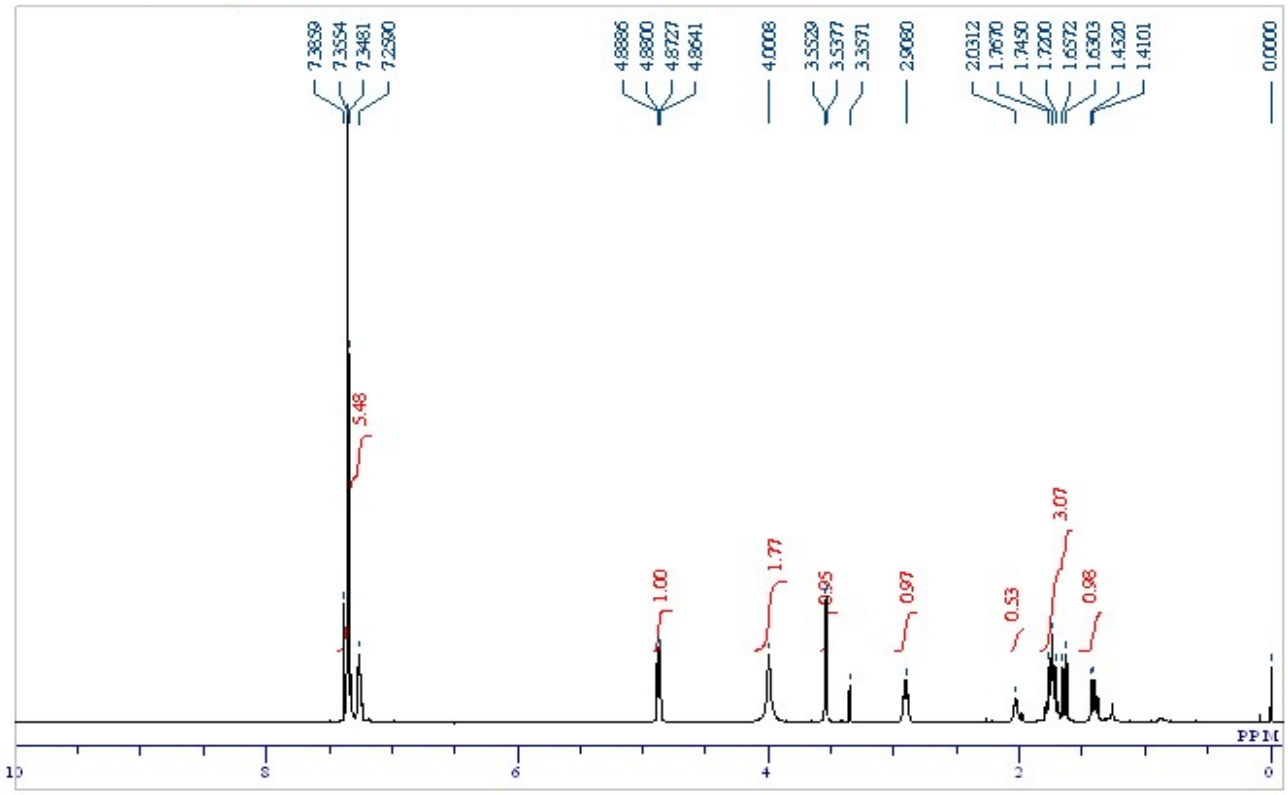
^{1}H-NMR of **174** in $CDCl_3$ at 20°C



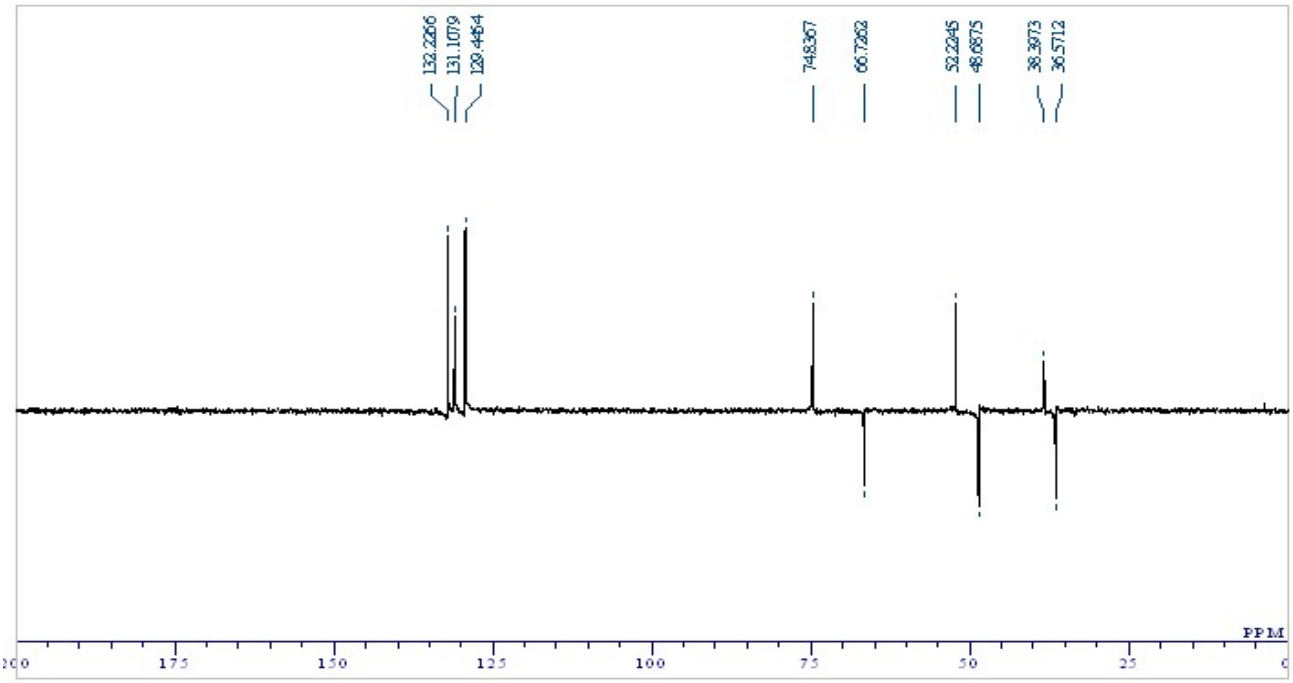
^{13}C-NMR of **174** in $CDCl_3$ at 20°C



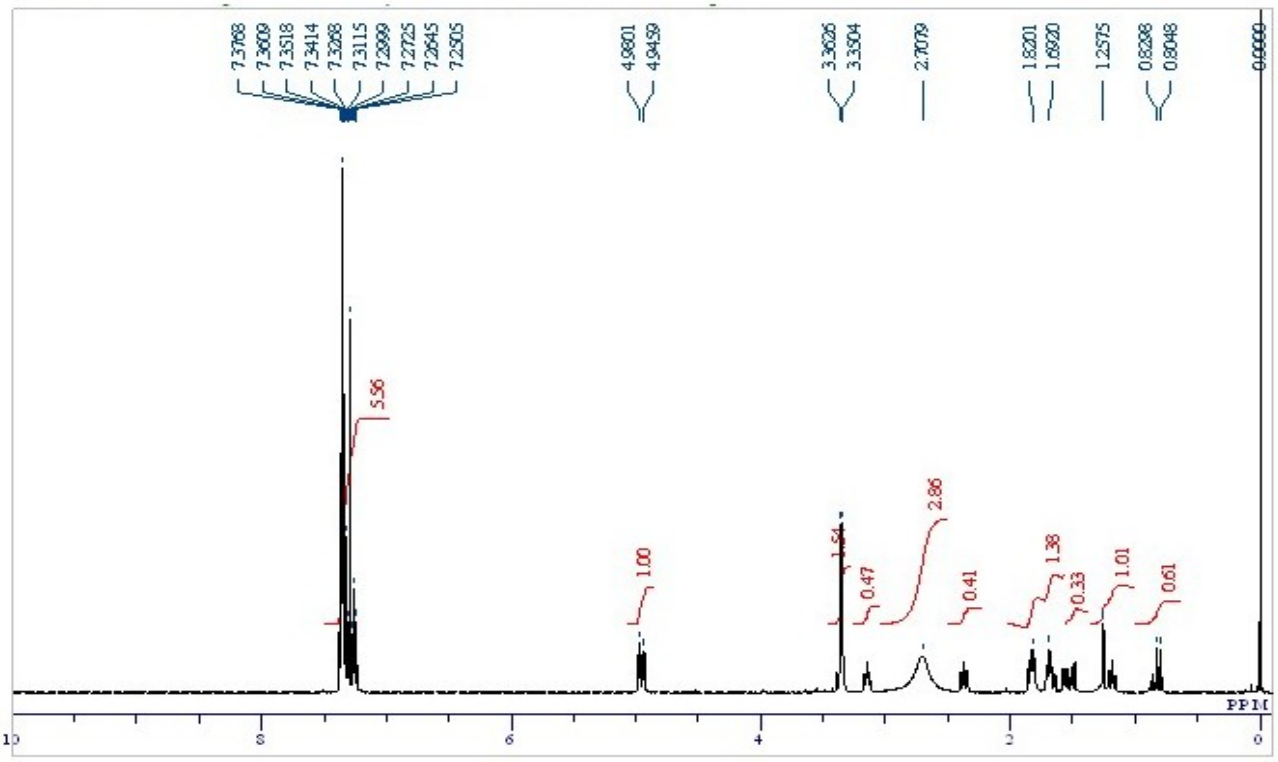
^{1}H-NMR of **175** in $CDCl_3$ at 20°C



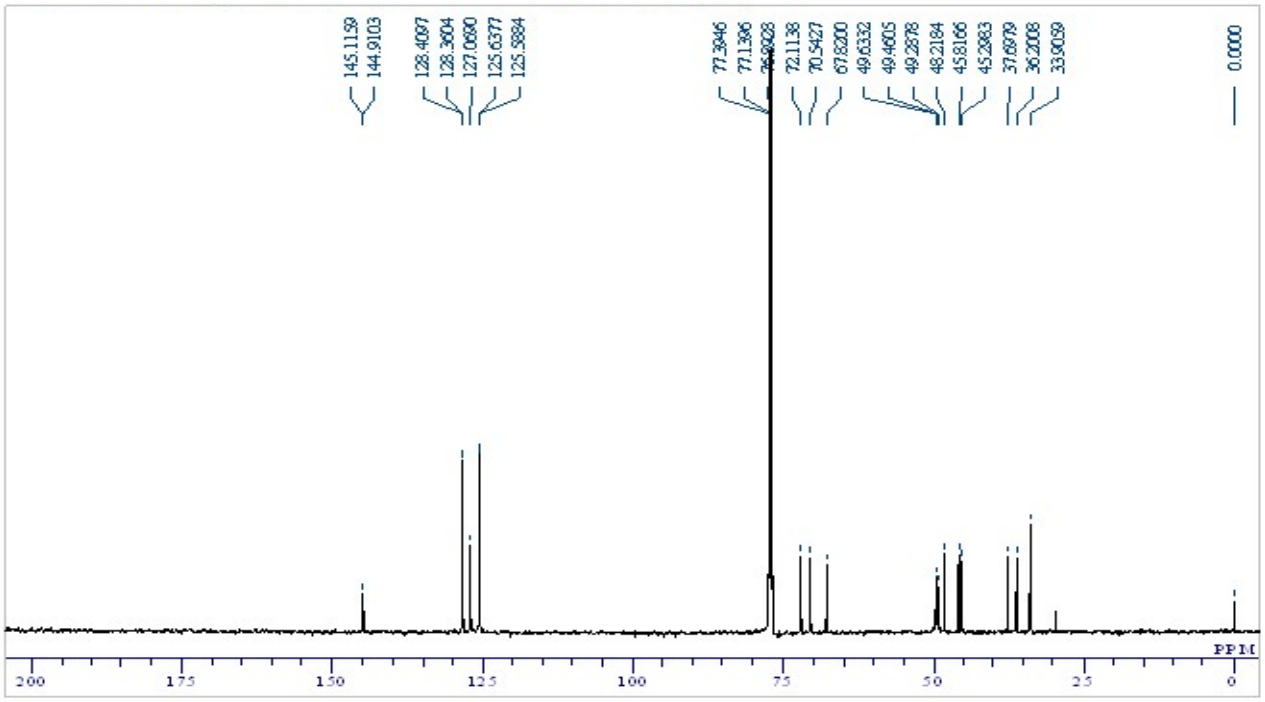
^{1}H-NMR of **180** in $CDCl_3$ at 20°C



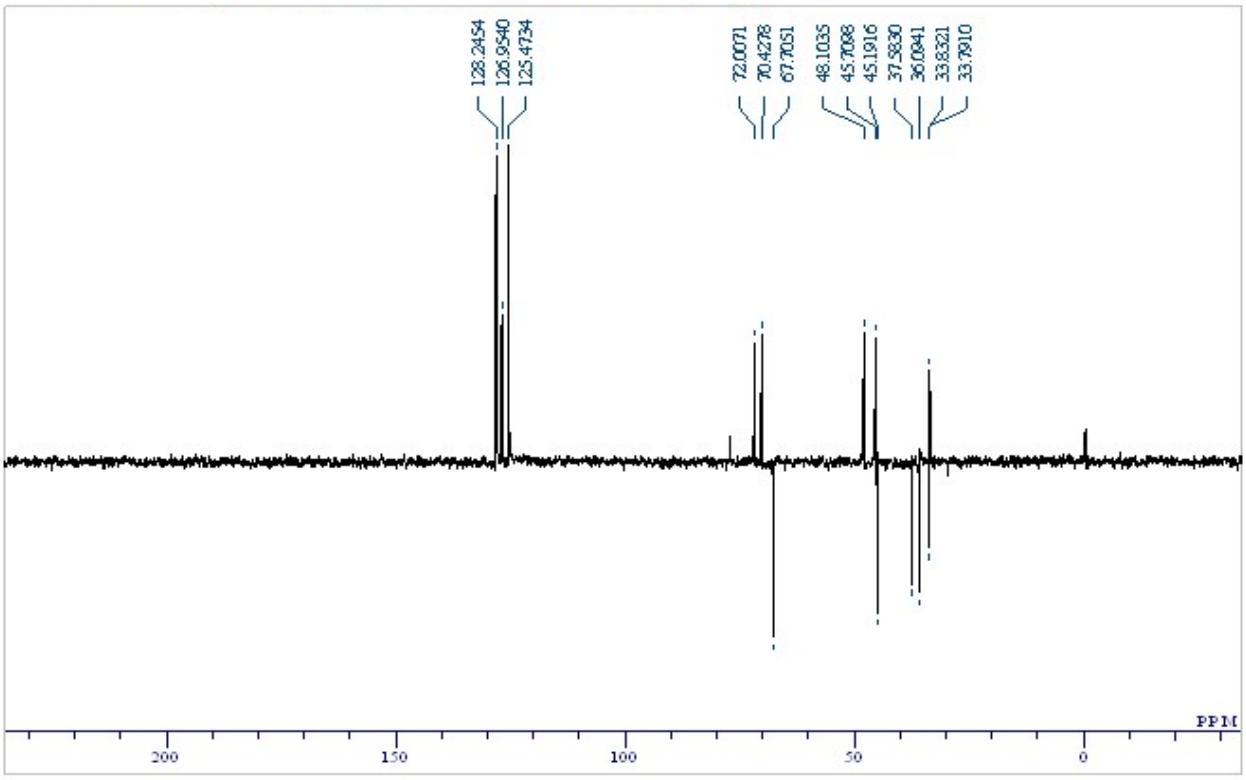
DEPT-NMR of **180** in $CDCl_3$ at 20°C



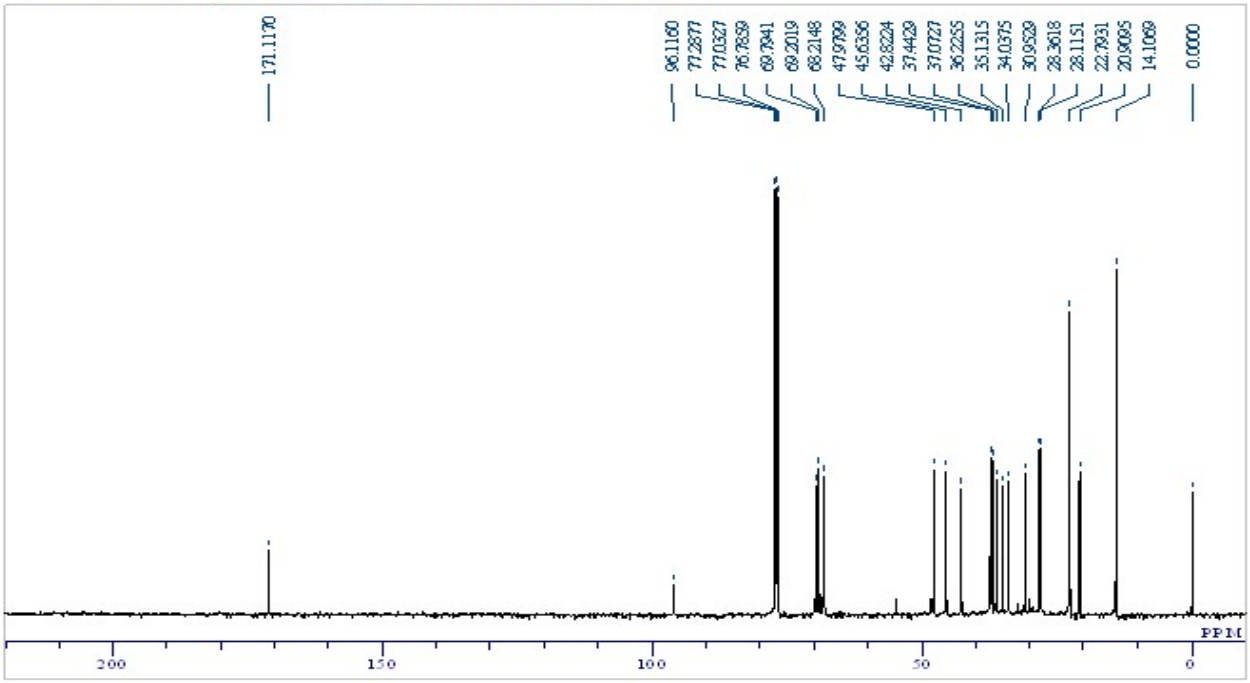
^{1}H-NMR of **179** in $CDCl_3$ at 20°C



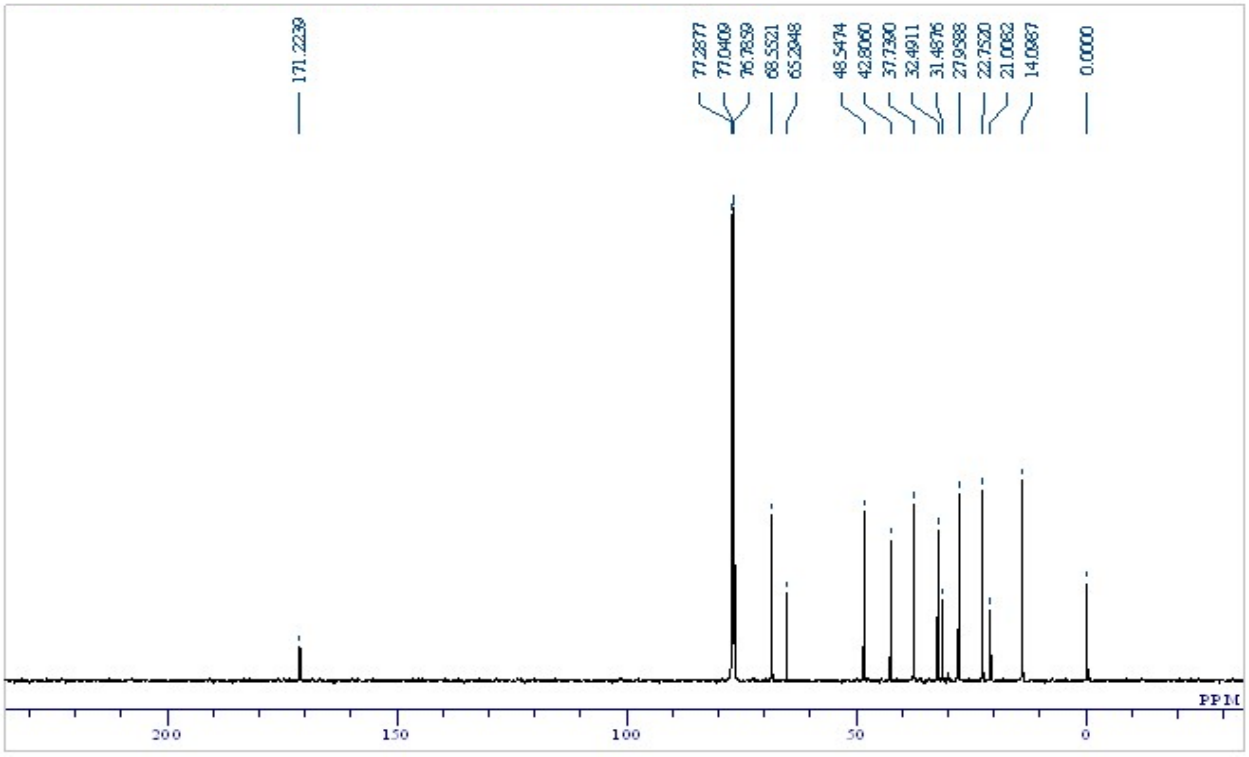
^{13}C-NMR of **179** in $CDCl_3$ at 20°C



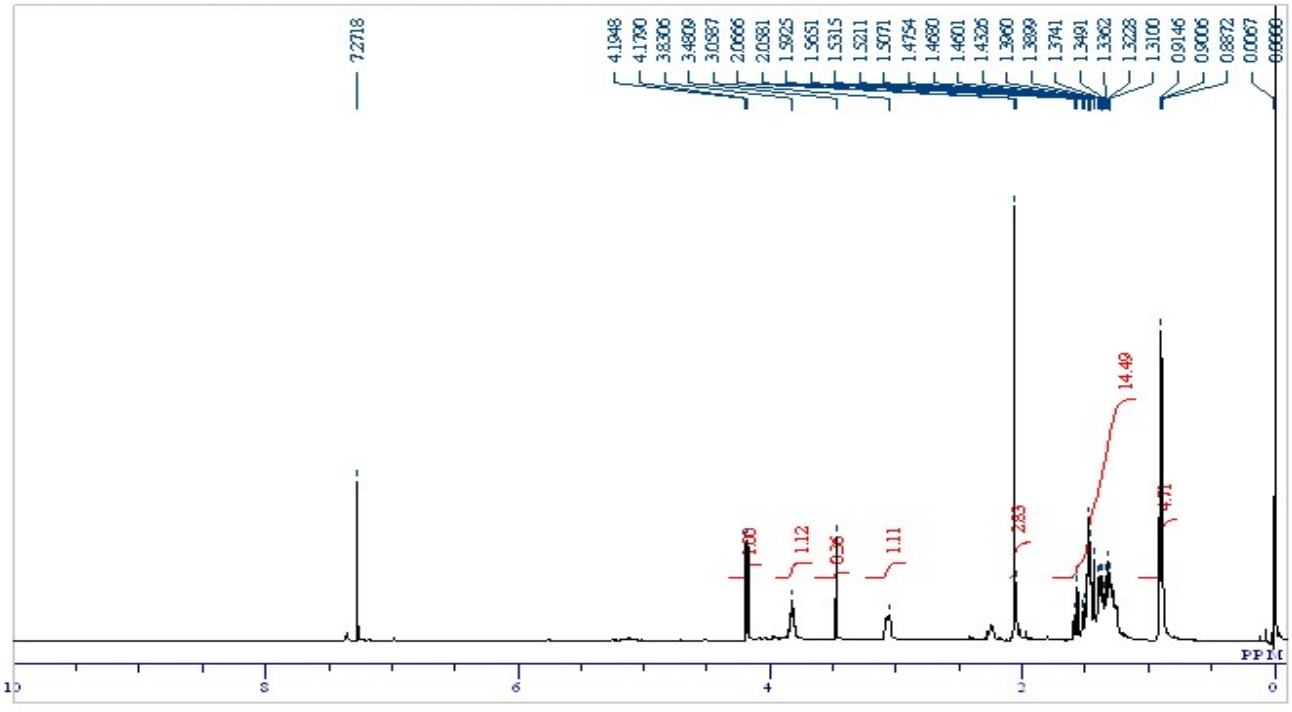
DEPT-NMR of **179** in $CDCl_3$ at 20°C



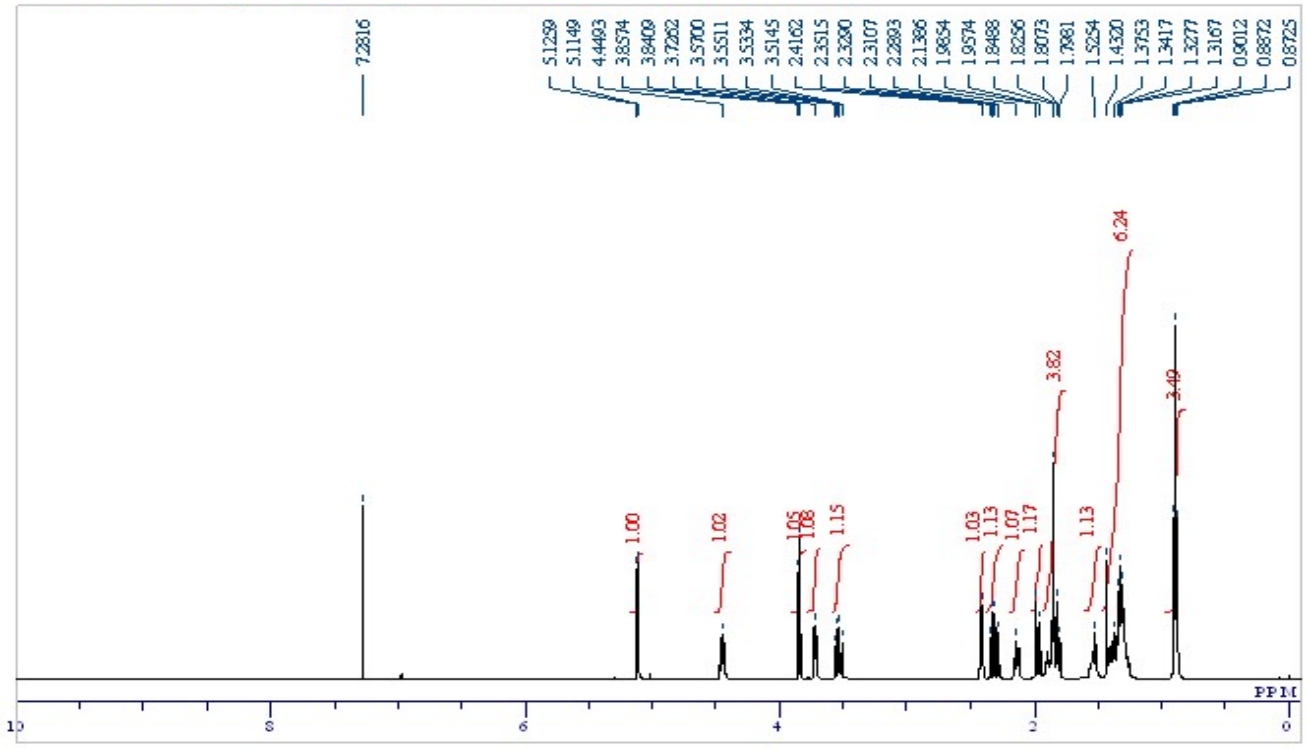
^{13}C-NMR of **177** in $CDCl_3$ at 20°C



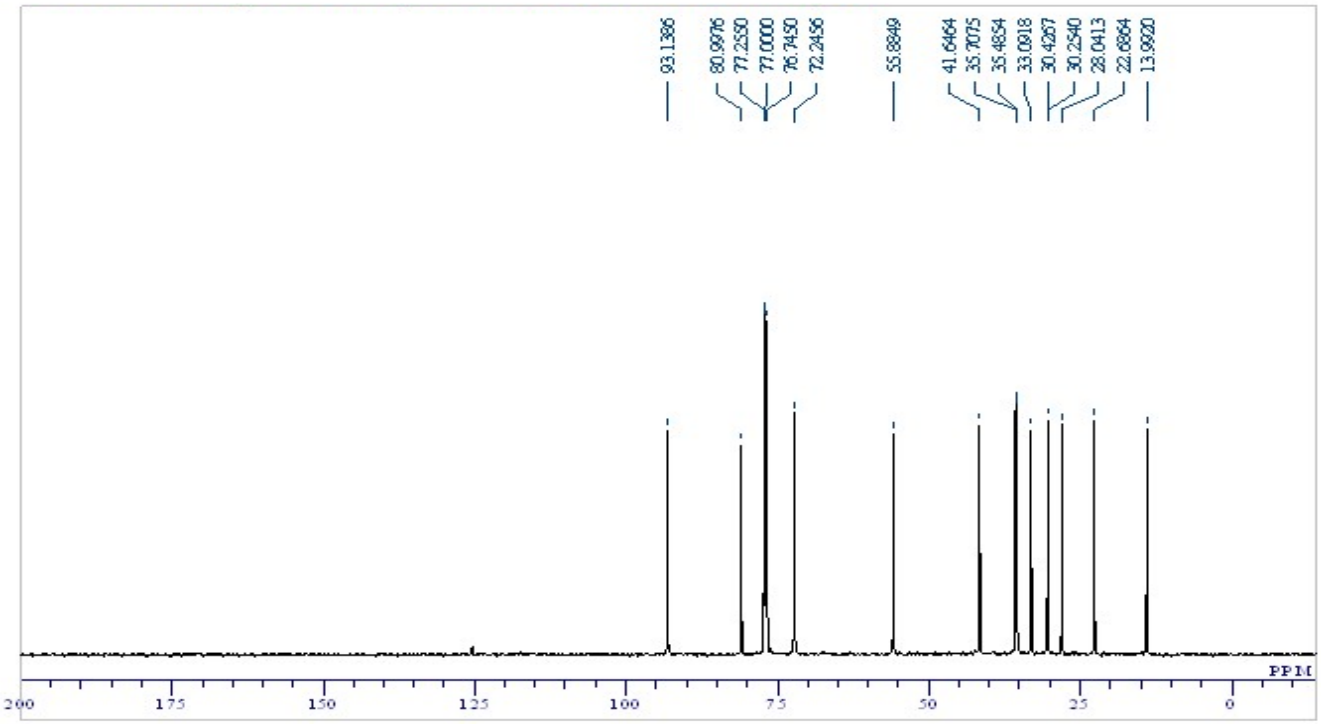
^{13}C-NMR of **178** in $CDCl_3$ at 20°C



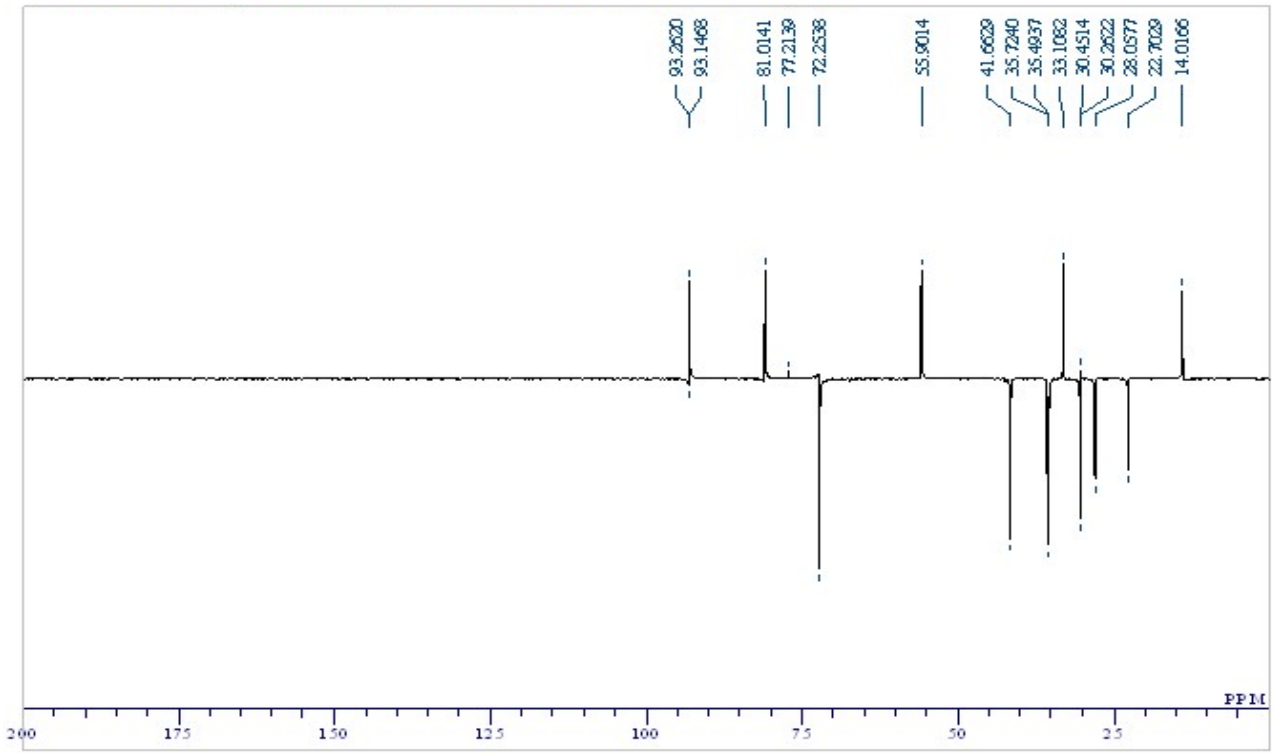
^{1}H-NMR of **178** in $CDCl_3$ at 20°C



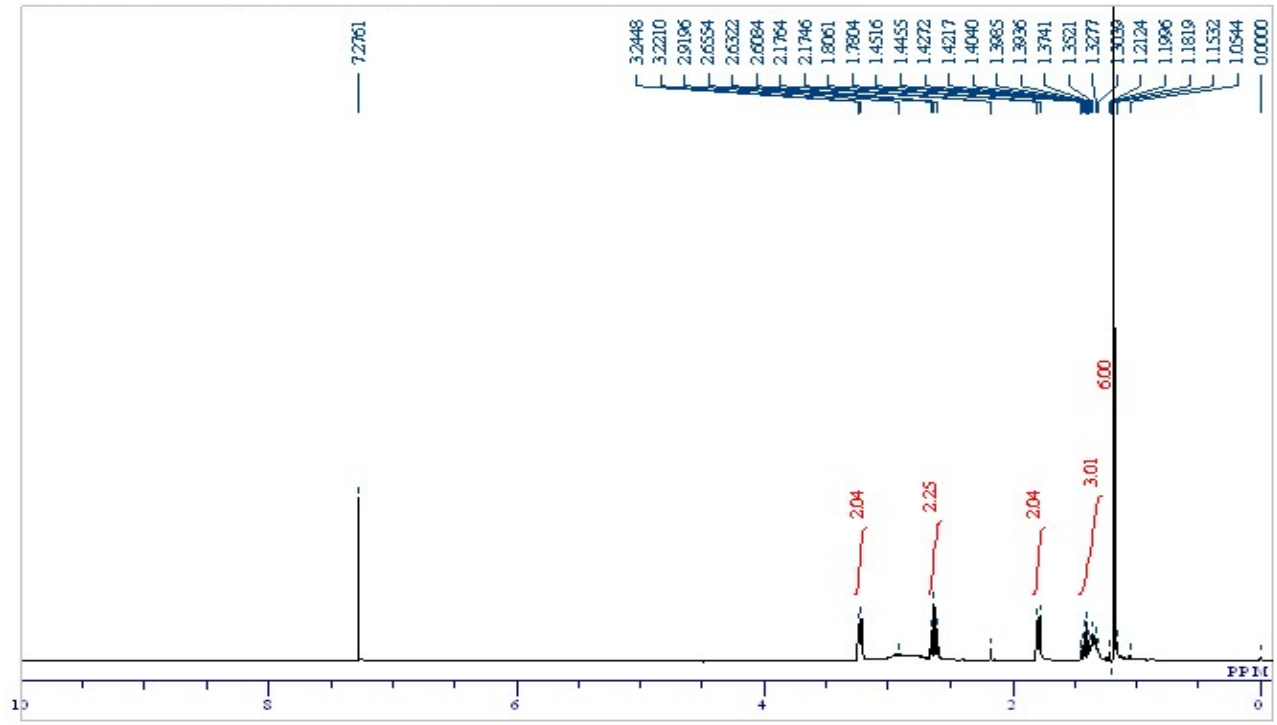
^{1}H-NMR of **218a** in $CDCl_3$ at 20°C



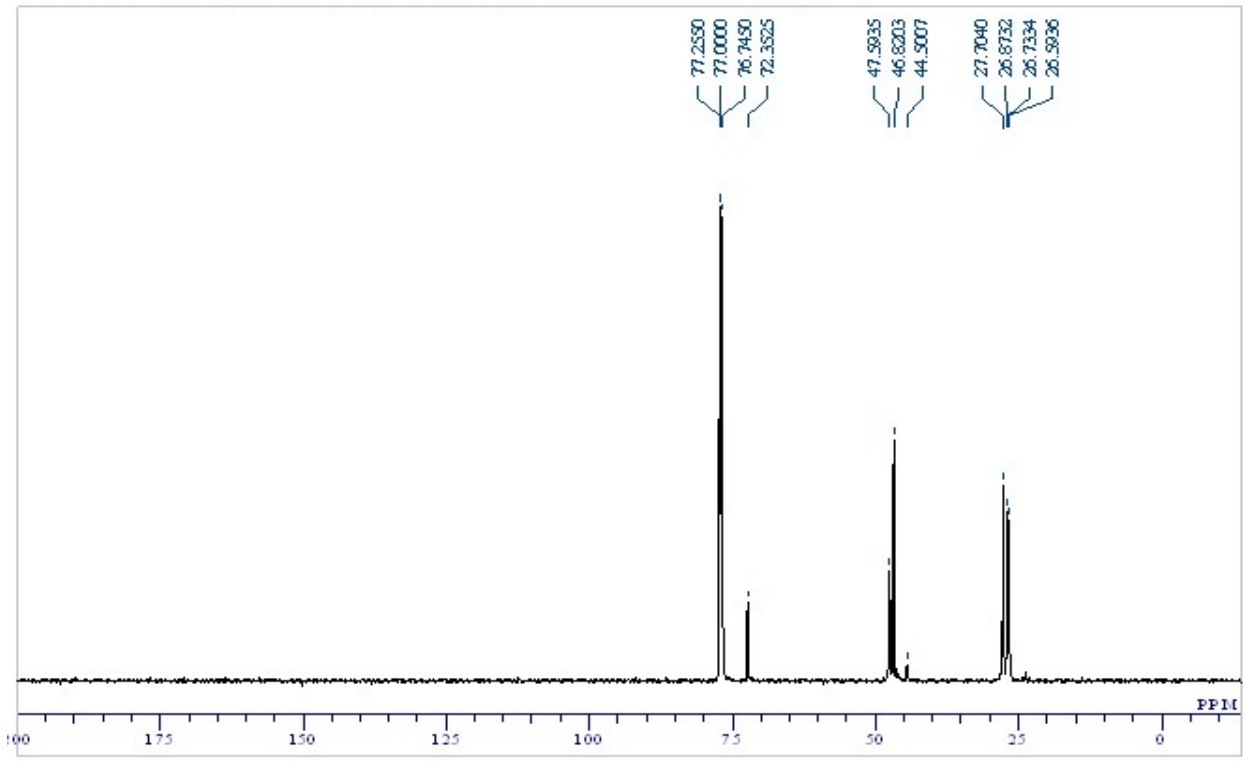
^{13}C-NMR of **218a** in $CDCl_3$ at 20°C



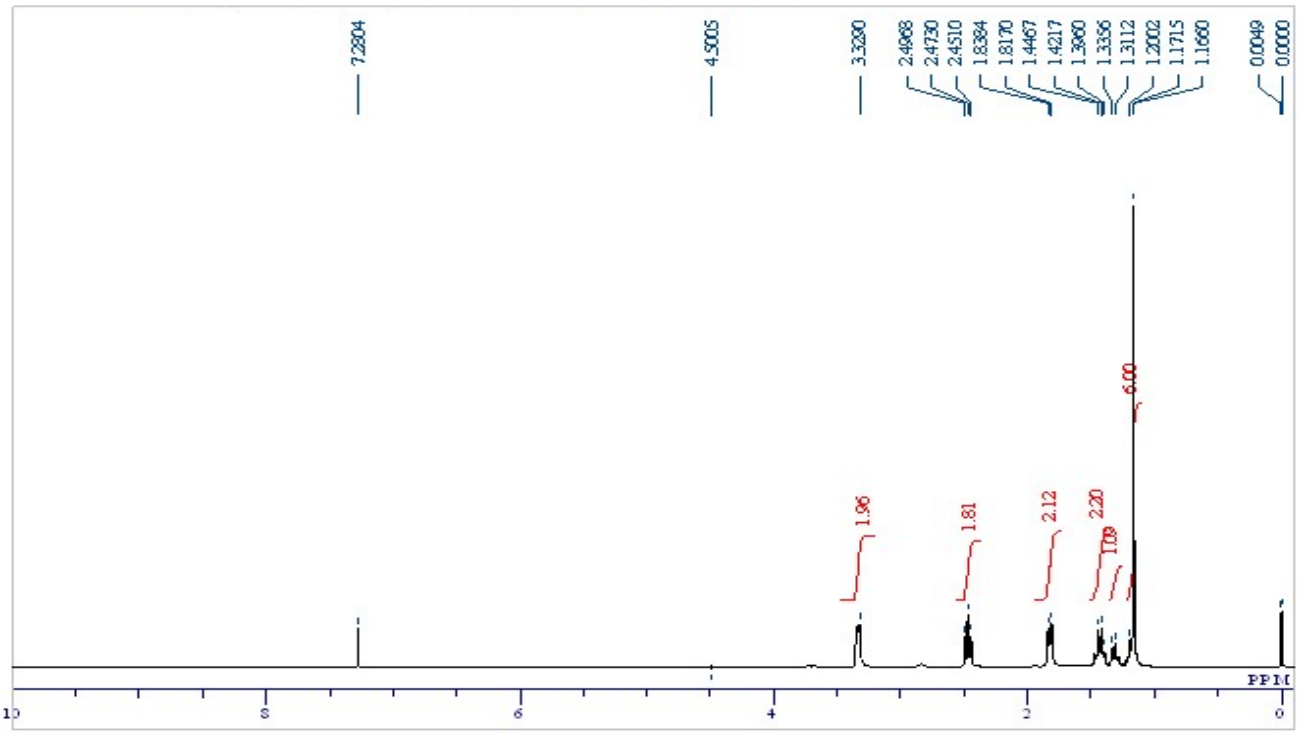
DEPT-NMR of **218a** in $CDCl_3$ at 20°C



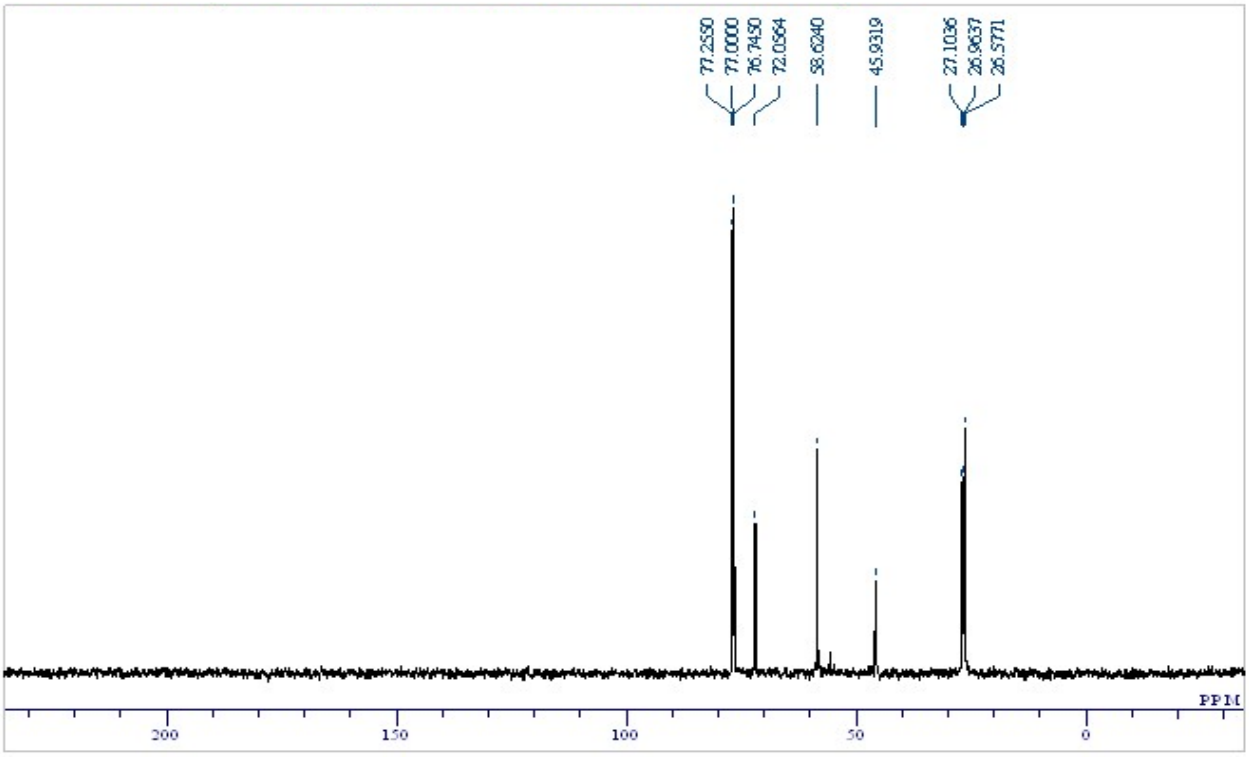
^{1}H-NMR of **190** in $CDCl_3$ at 20°C



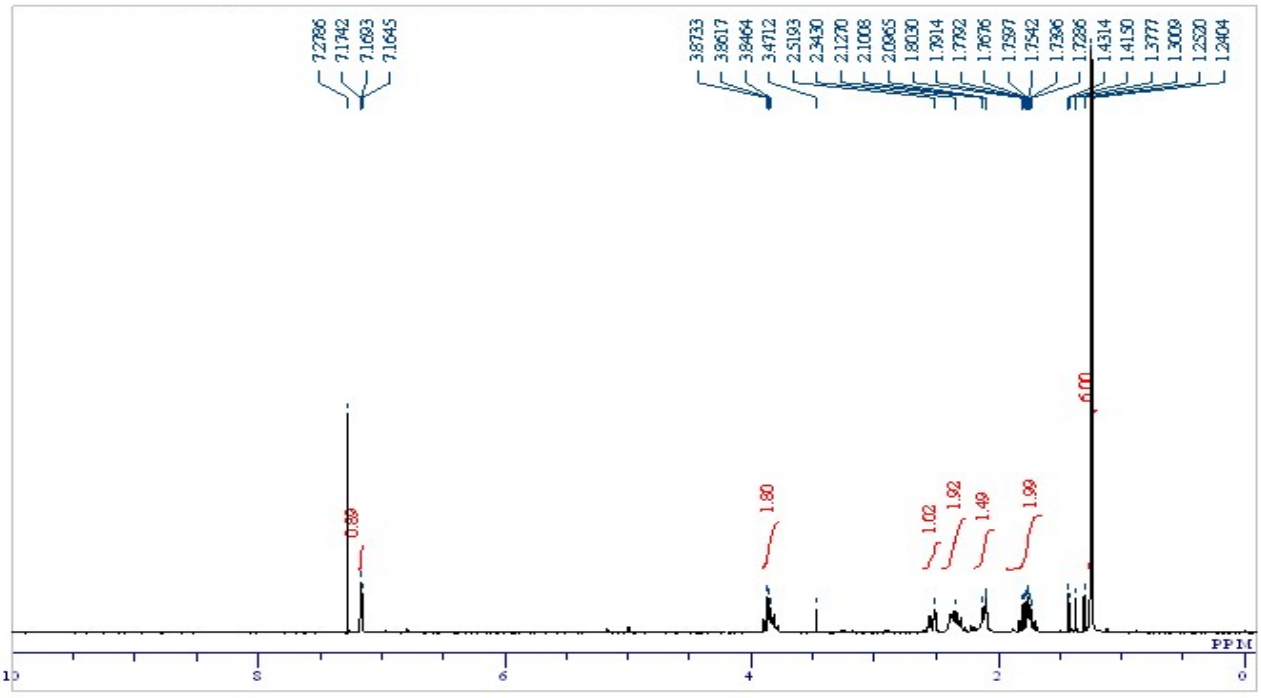
^{13}C-NMR of **190** in $CDCl_3$ at 20°C



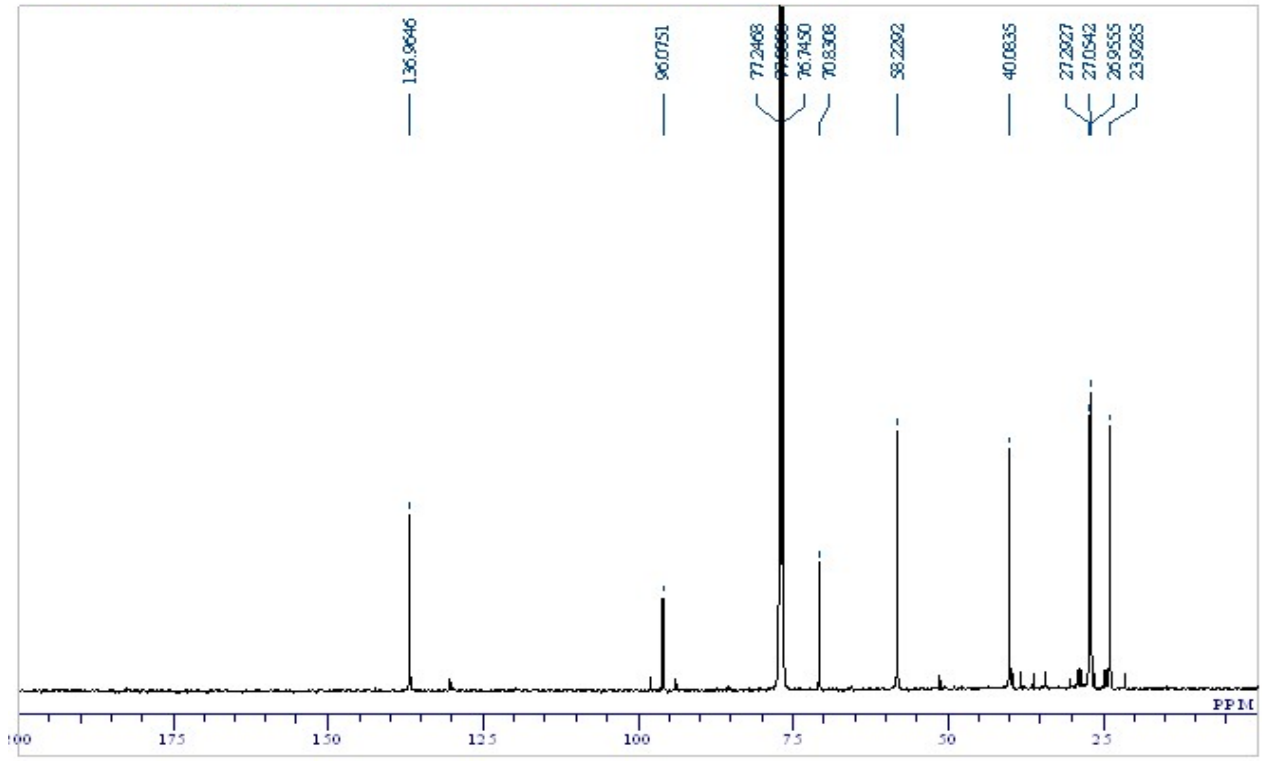
^{1}H-NMR of **191** in $CDCl_3$ at 20°C



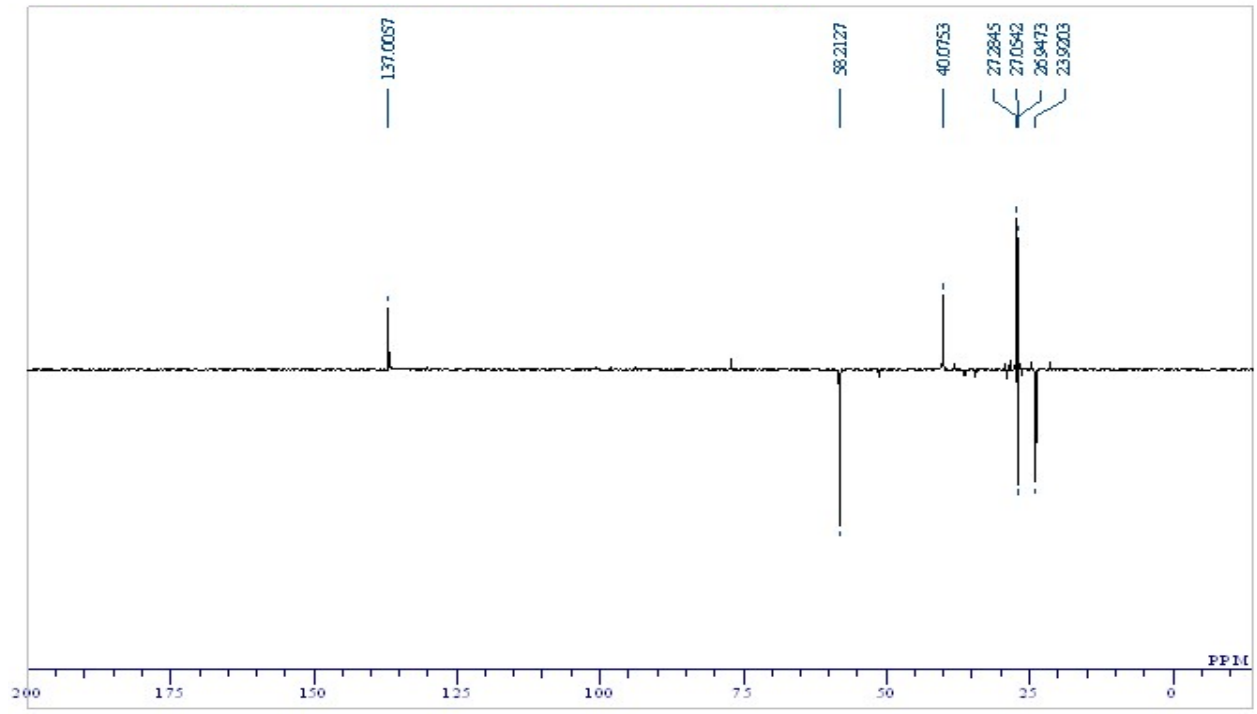
^{13}C-NMR of **191** in $CDCl_3$ at 20°C



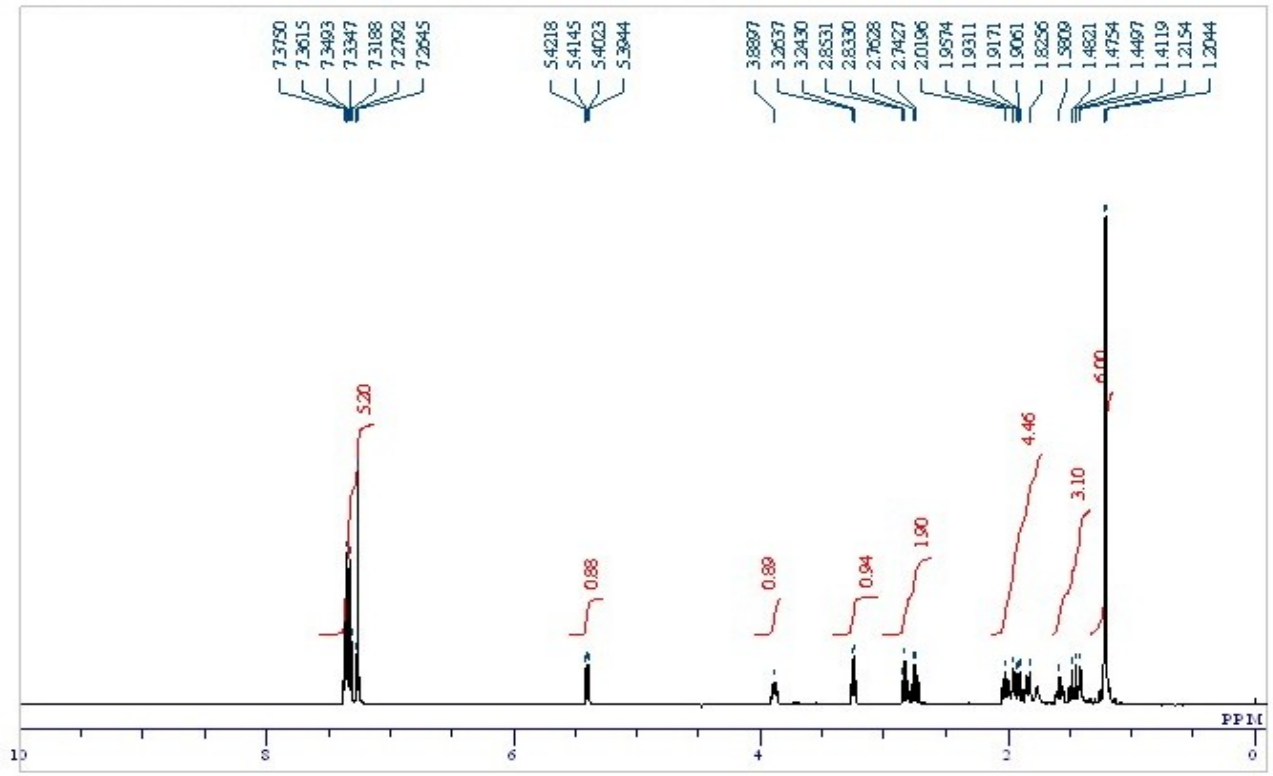
^{1}H-NMR of **192** in $CDCl_3$ at 20°C



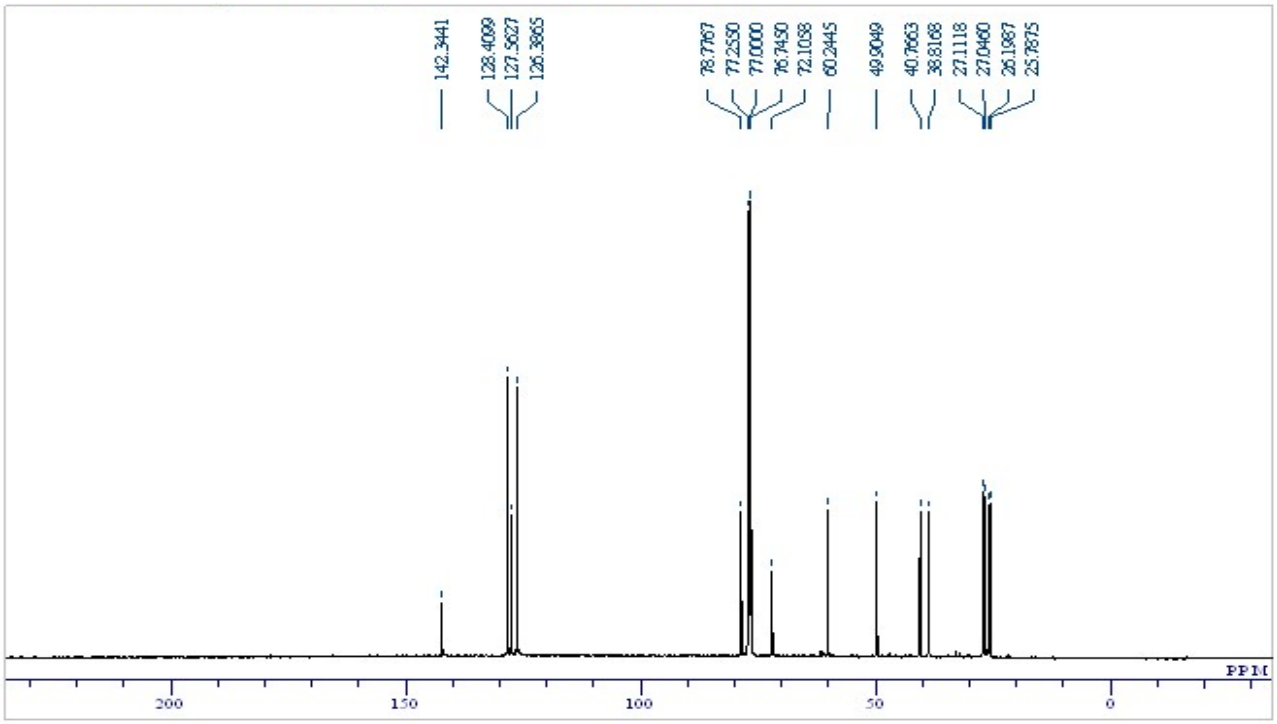
^{13}C-NMR of **192** in $CDCl_3$ at 20°C



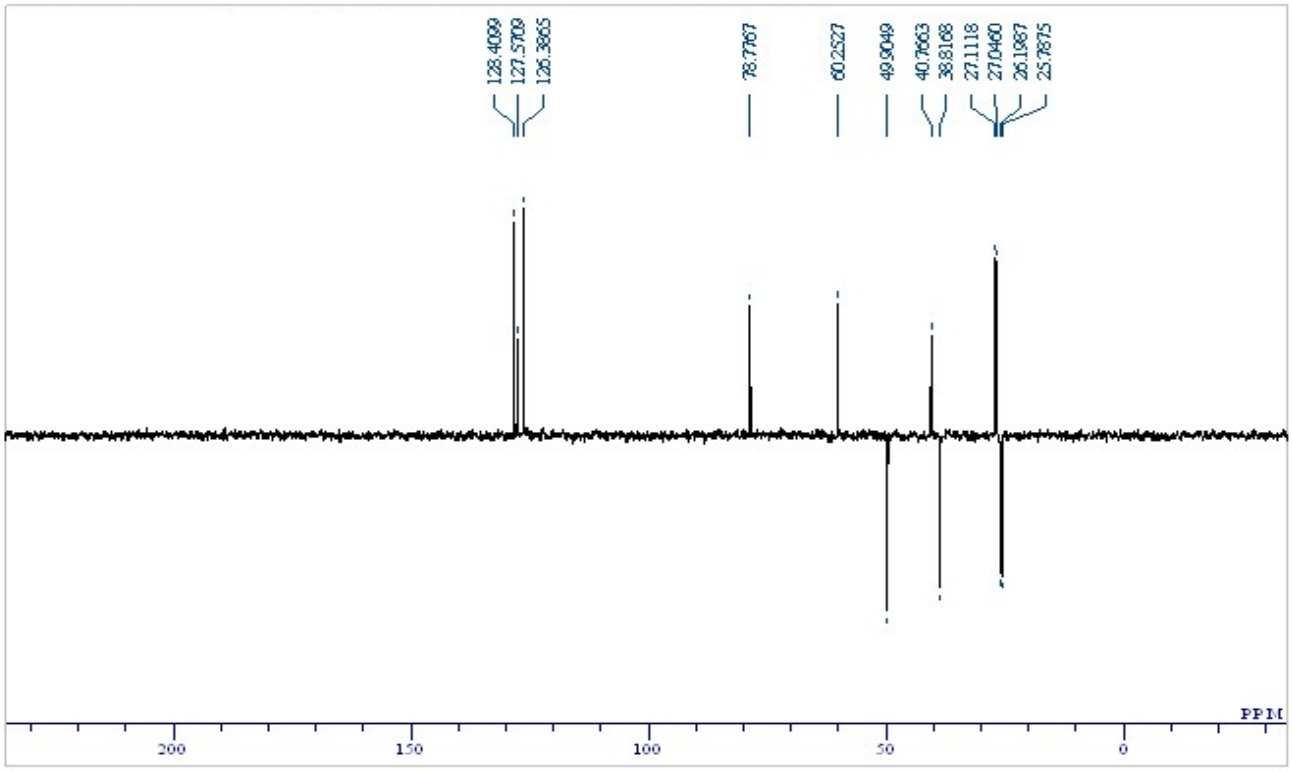
DEPT-NMR of **192** in $CDCl_3$ at 20°C



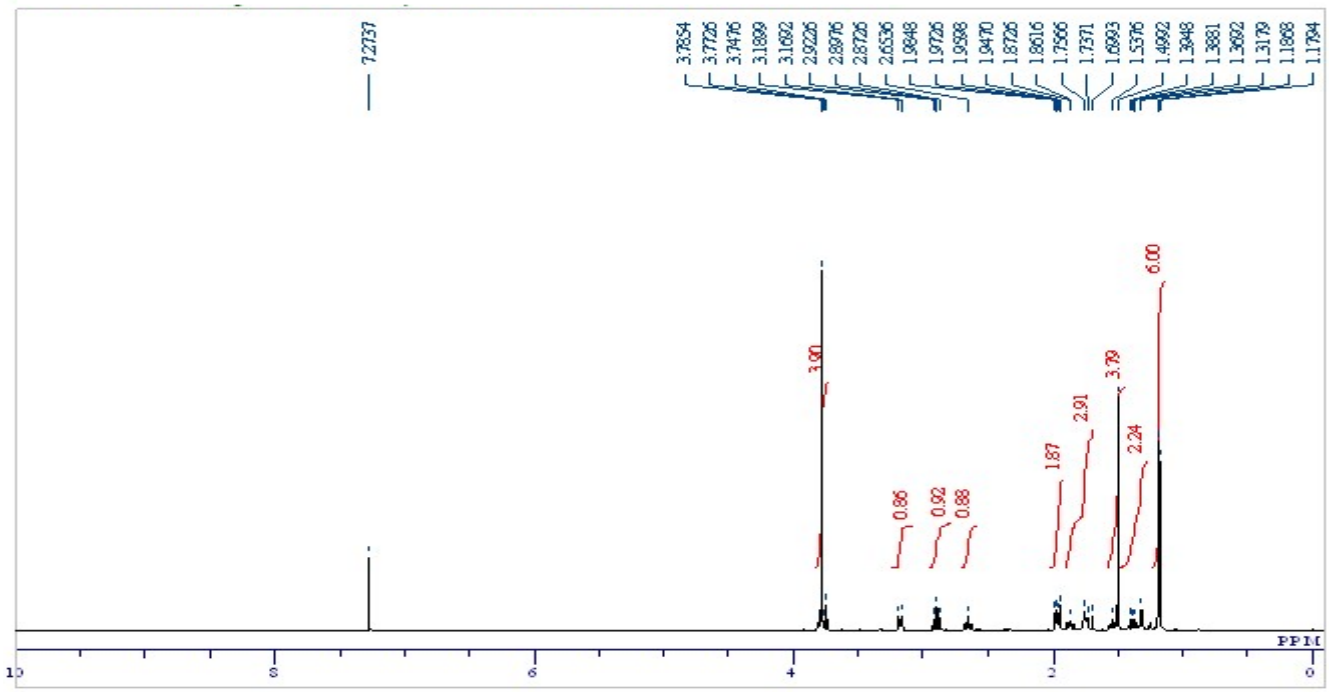
^{1}H-NMR of **194a** in $CDCl_3$ at 20°C



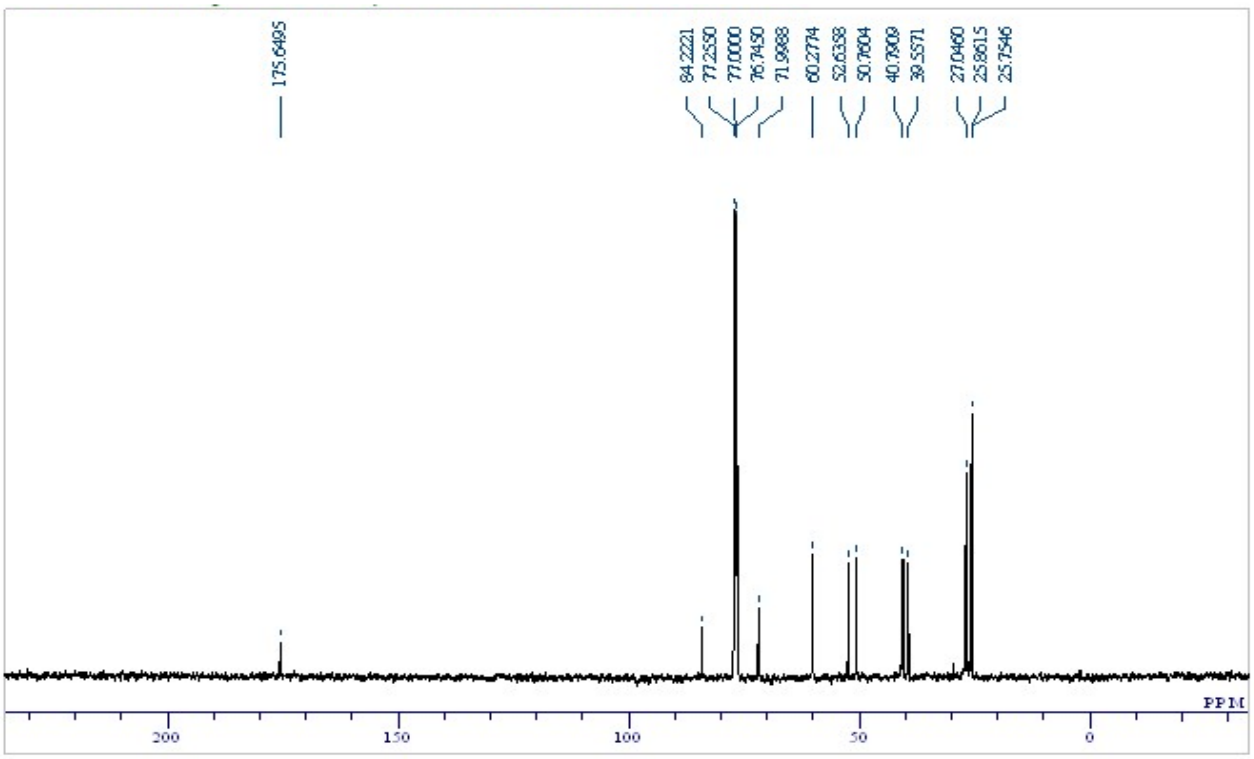
^{13}C-NMR of **194a** in $CDCl_3$ at 20°C



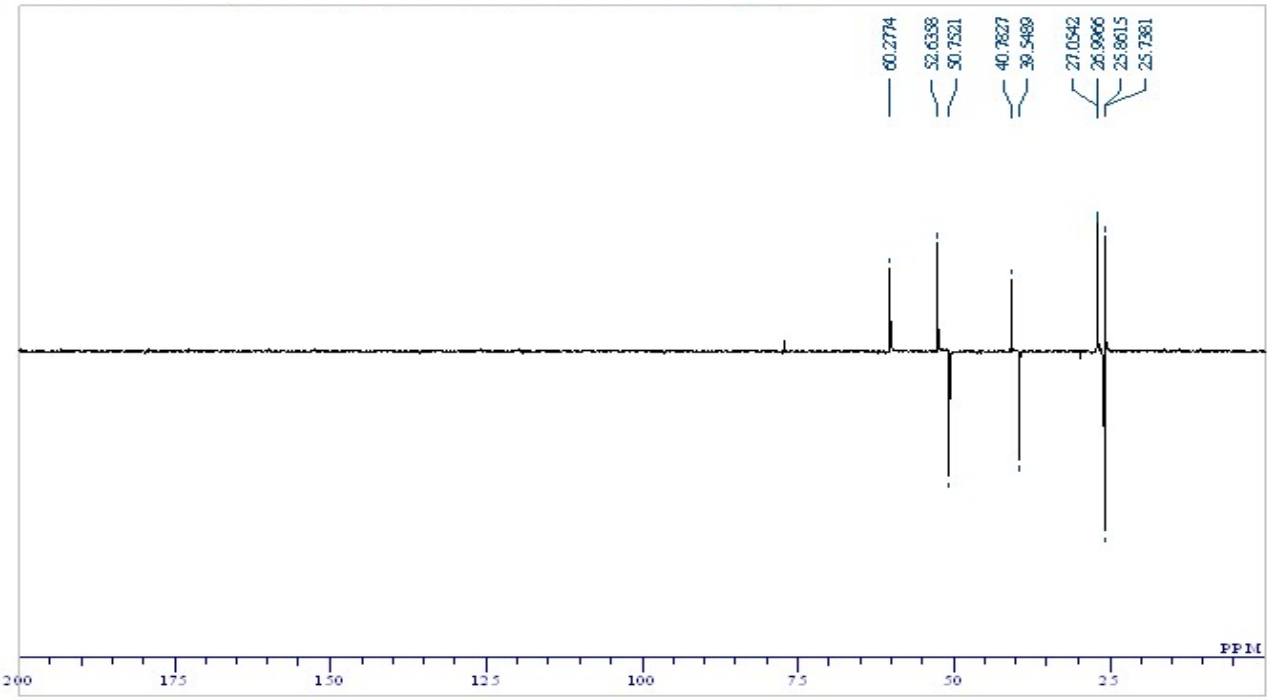
DEPT-NMR of **194a** in $CDCl_3$ at 20°C



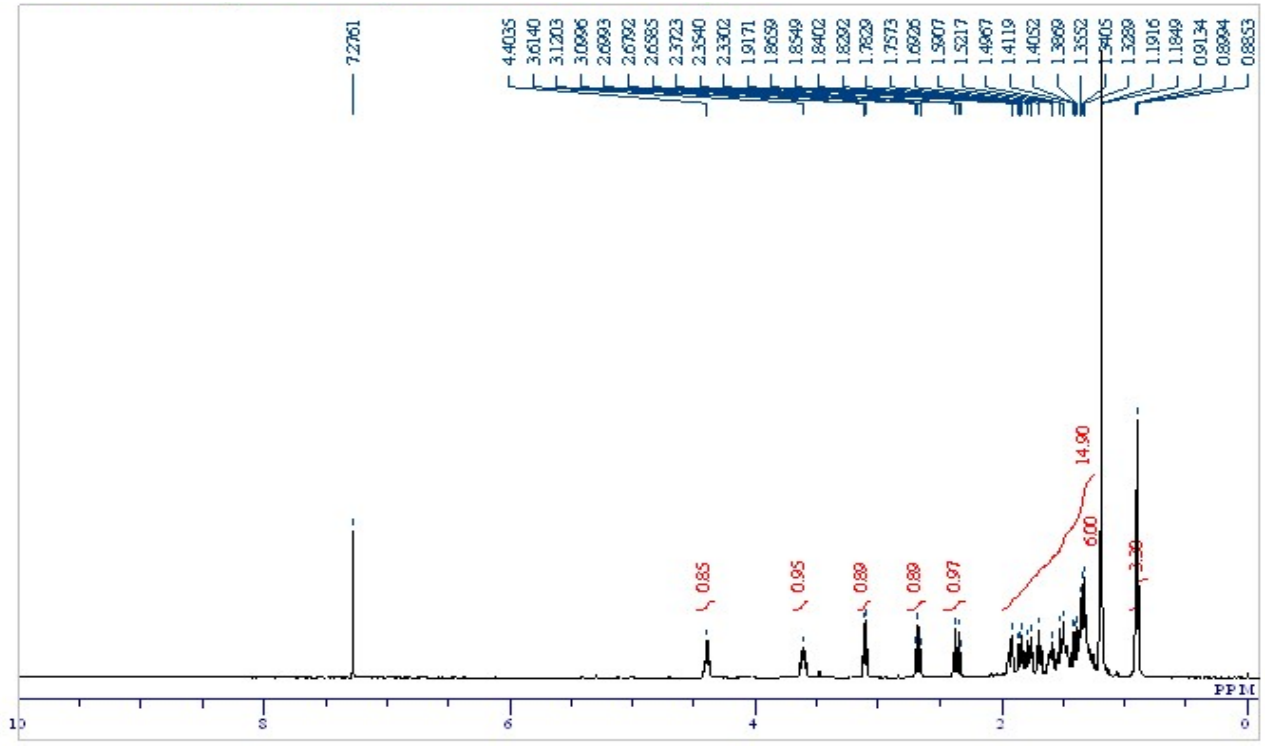
^{1}H-NMR of **196** in $CDCl_3$ at 20°C



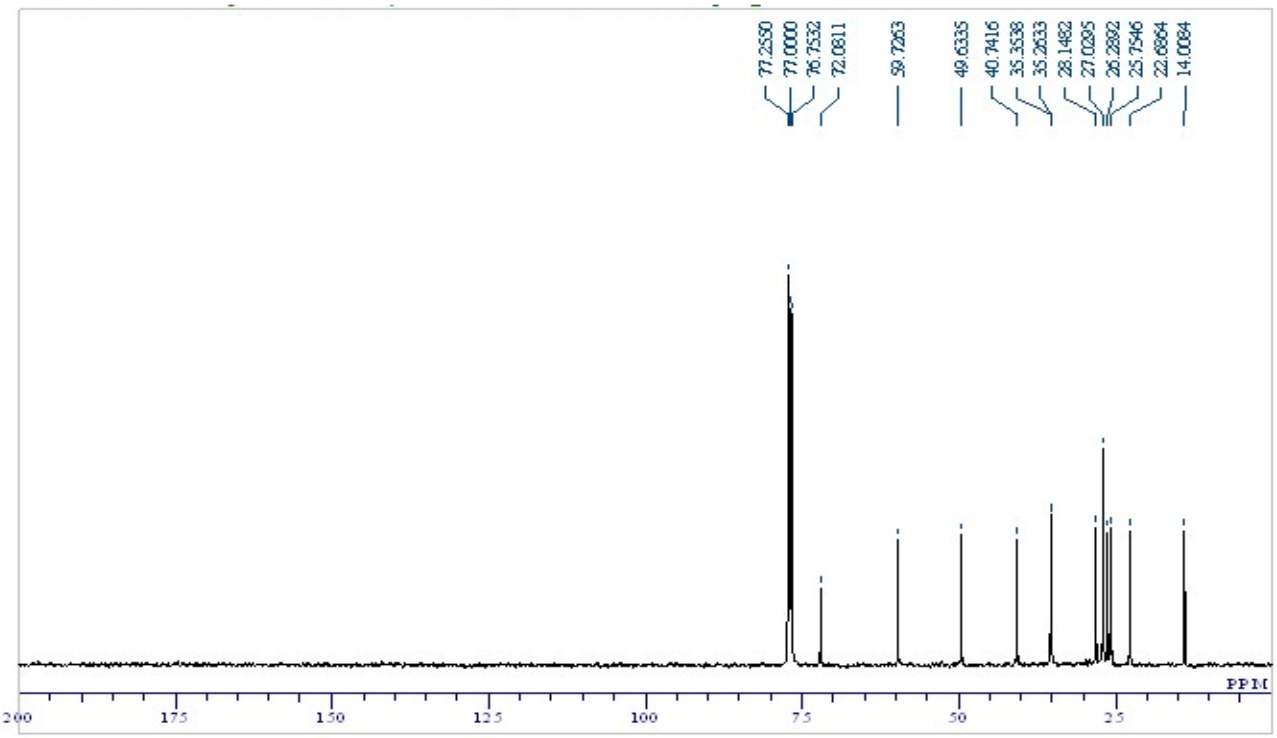
^{13}C-NMR of **196** in $CDCl_3$ at 20°C



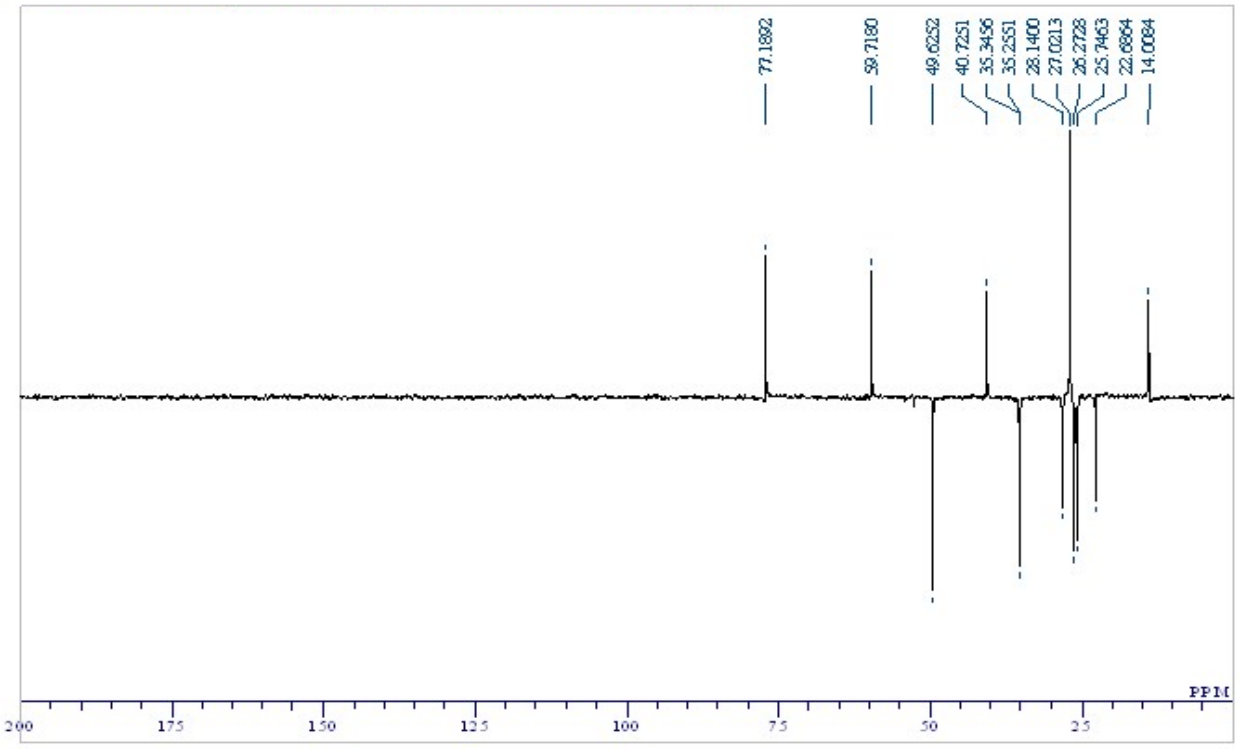
DEPT-NMR of **196** in $CDCl_3$ at 20°C



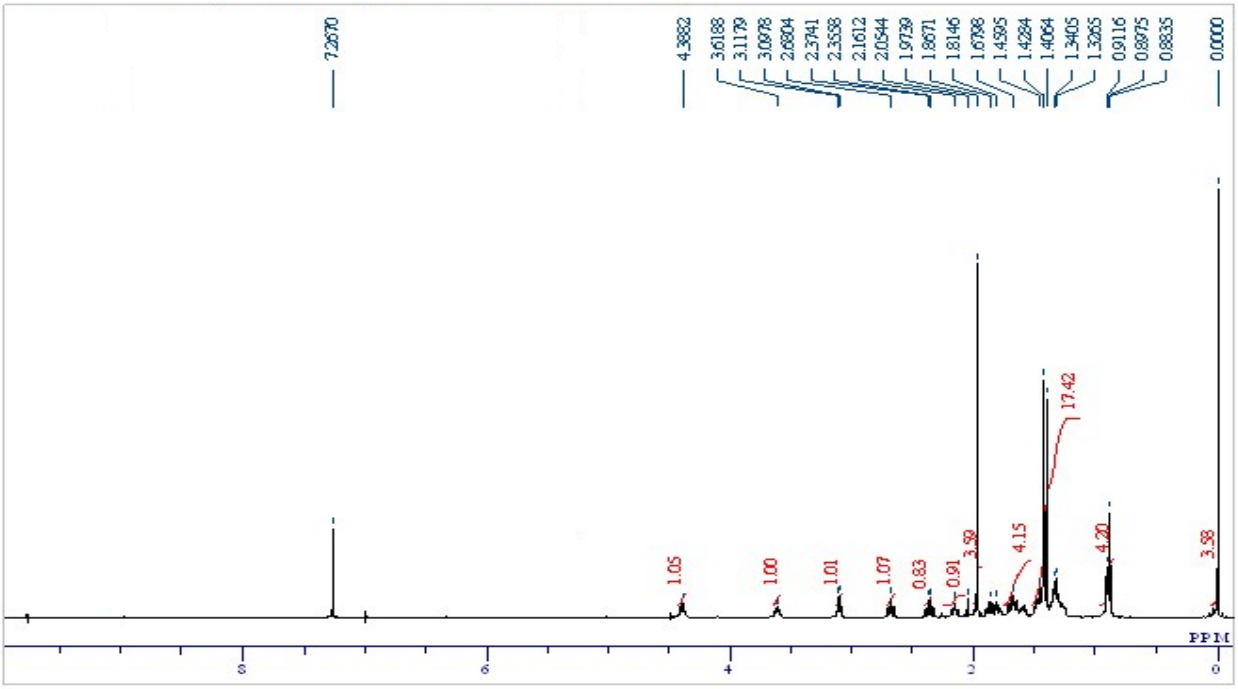
^{1}H-NMR of **194b** in $CDCl_3$ at 20°C



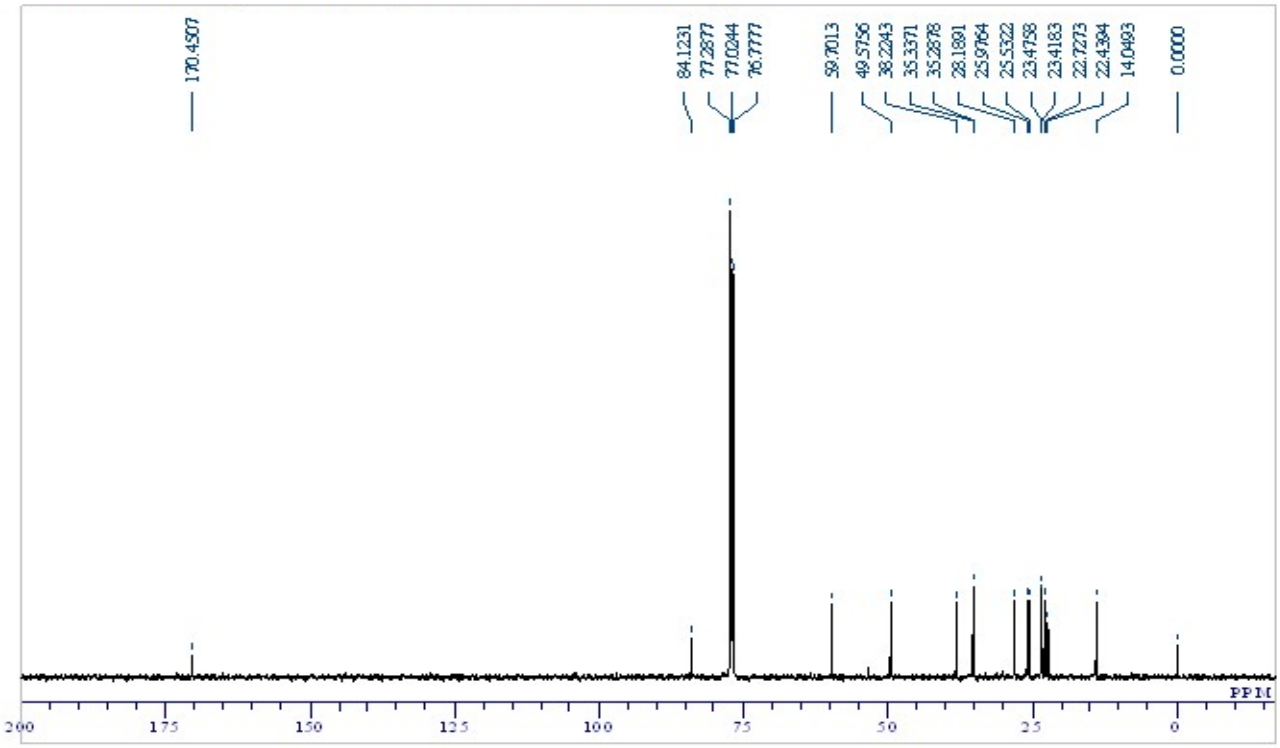
^{13}C-NMR of **194b** in $CDCl_3$ at 20°C



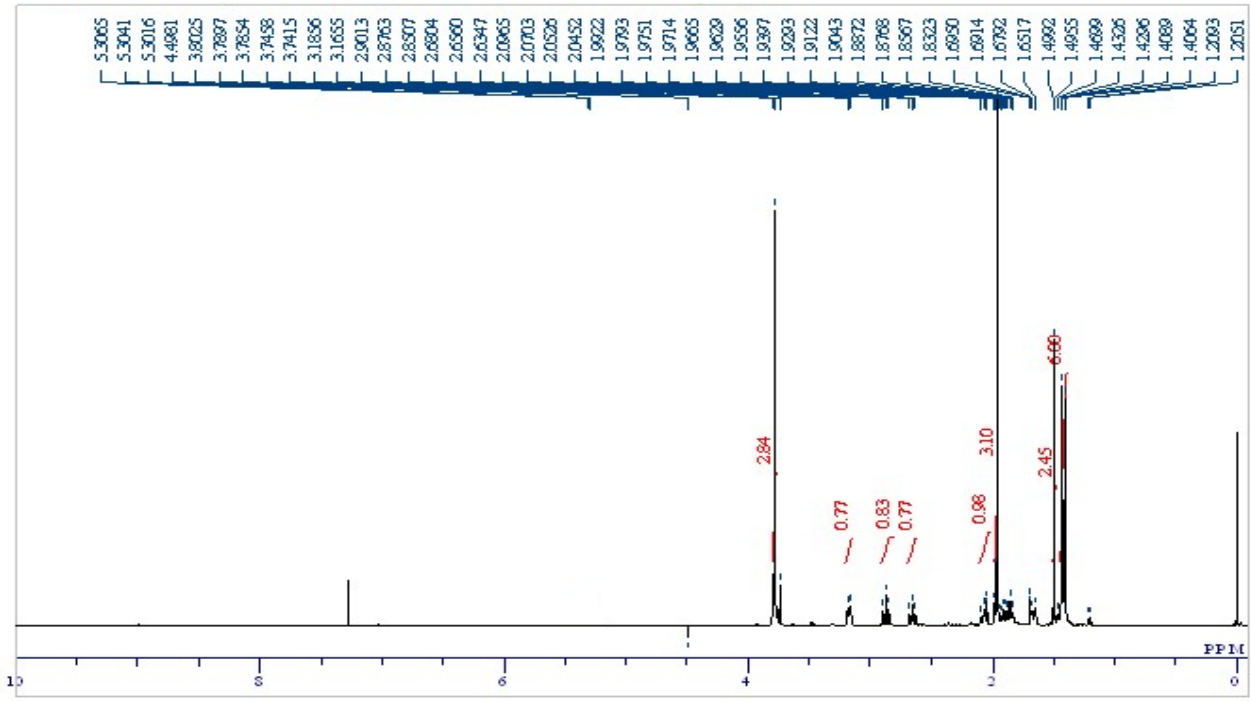
DEPT-NMR of **194b** in $CDCl_3$ at 20°C



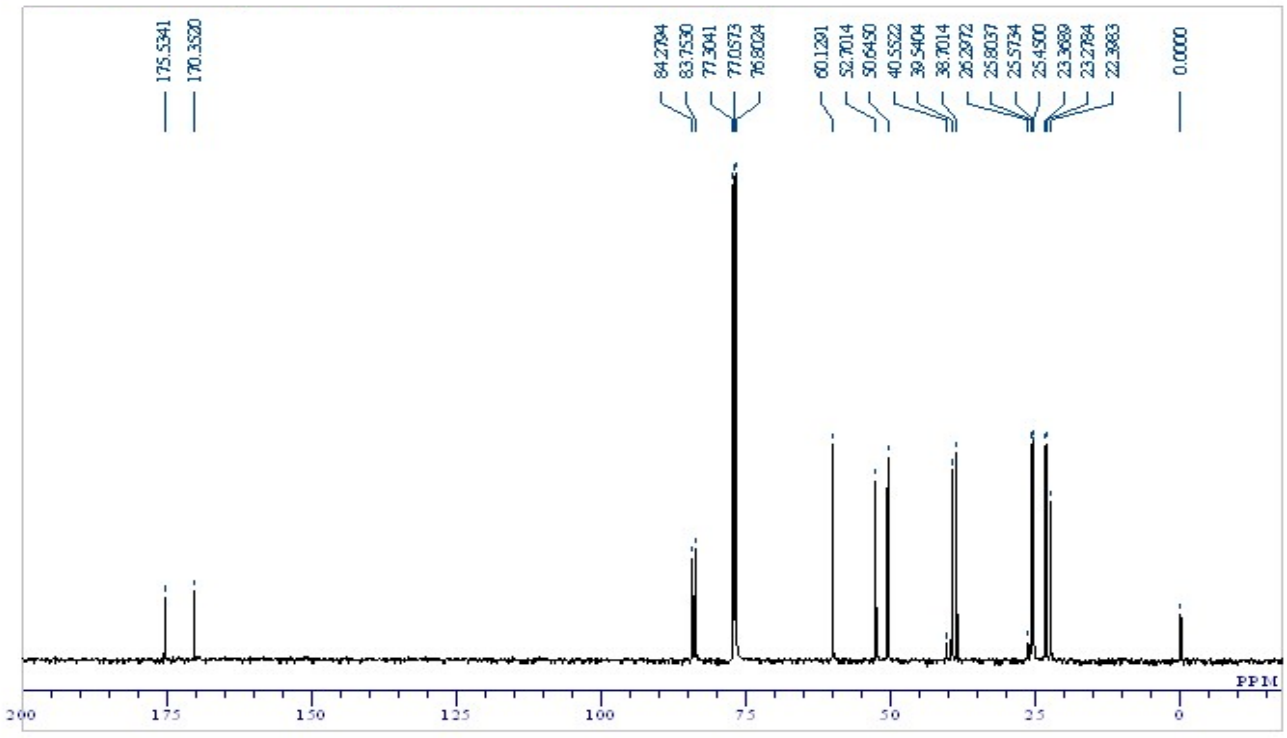
^{1}H-NMR of **199** in $CDCl_3$ at 20°C



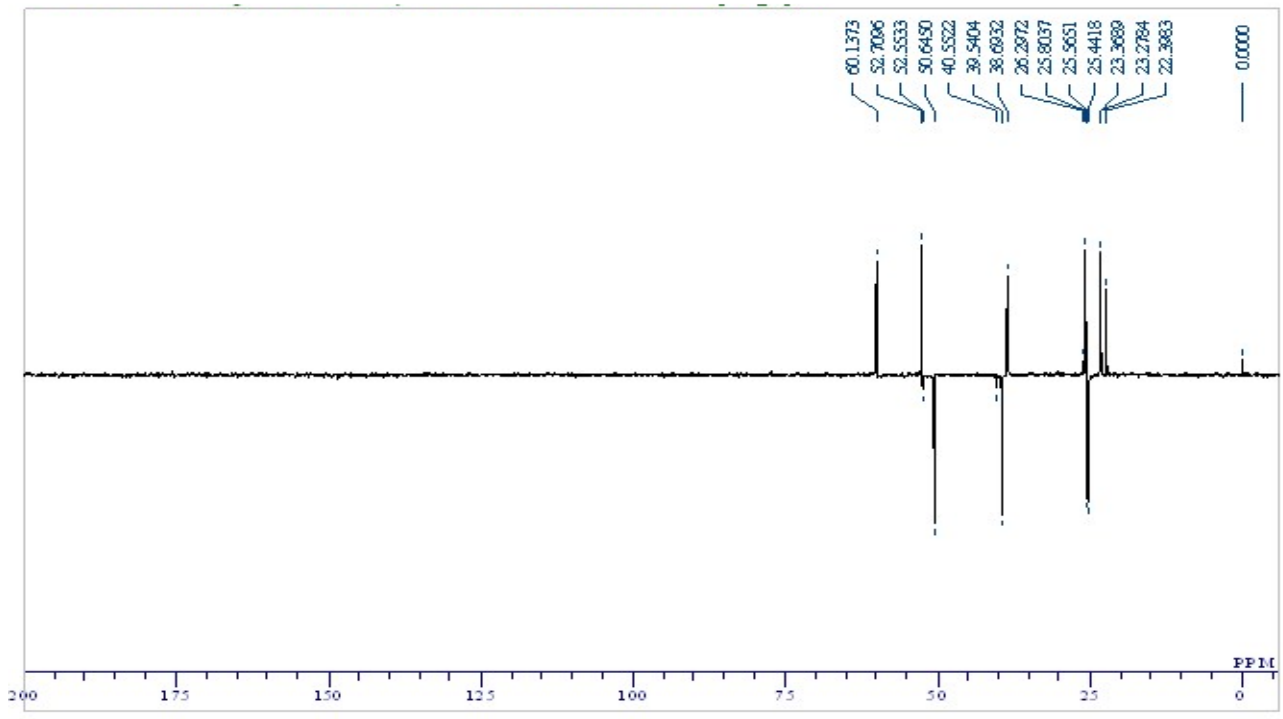
^{13}C-NMR of **199** in $CDCl_3$ at 20°C



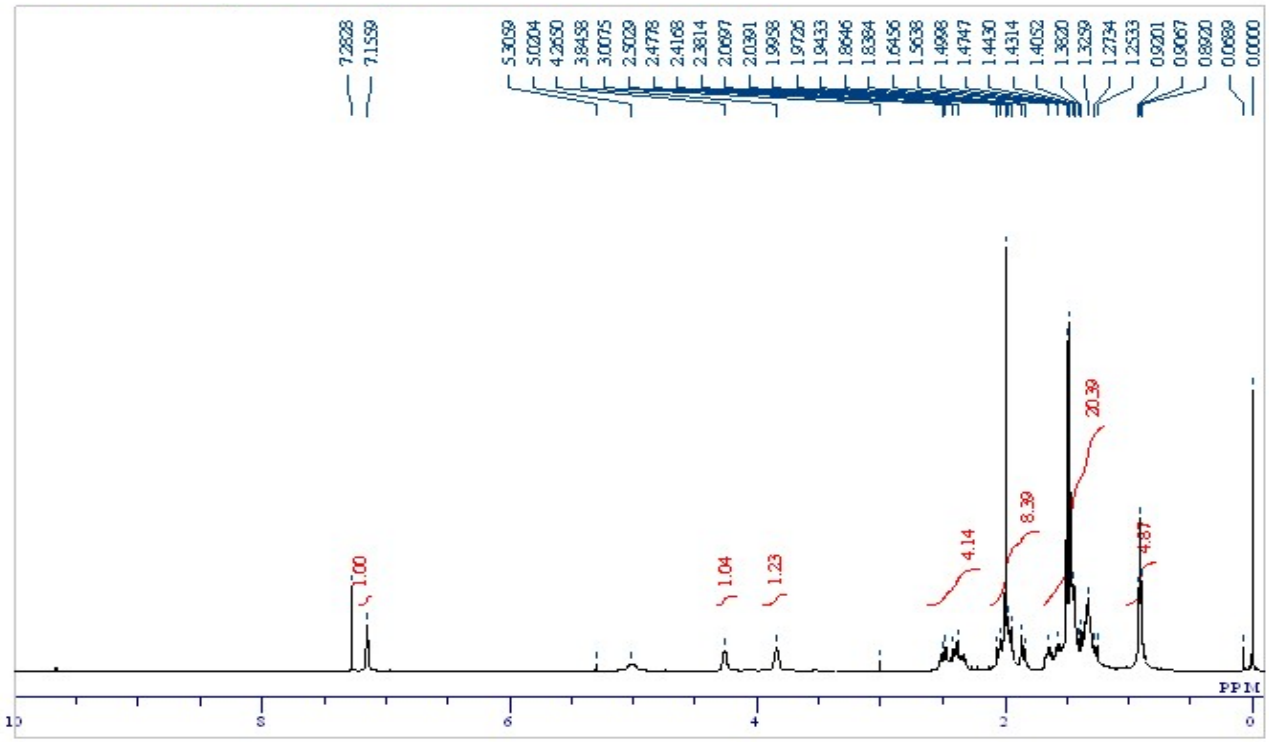
^{1}H-NMR of **200** in $CDCl_3$ at 20°C



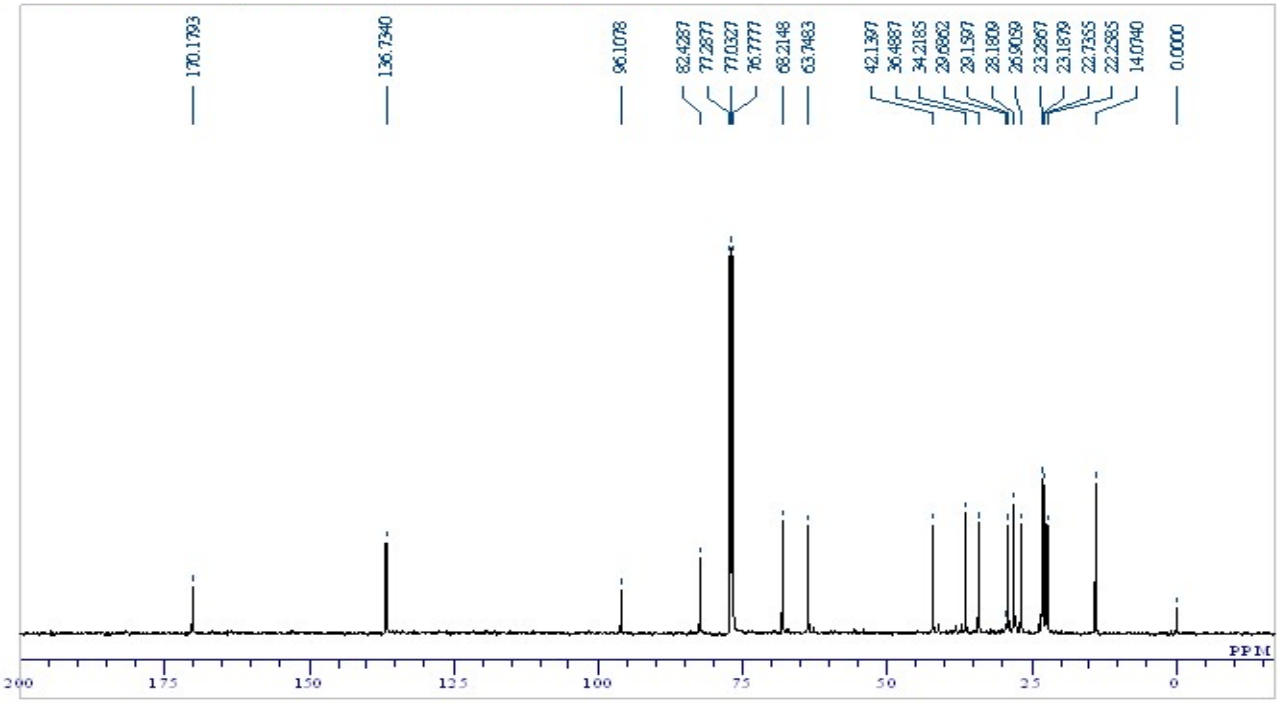
^{13}C-NMR of **200** in $CDCl_3$ at 20°C



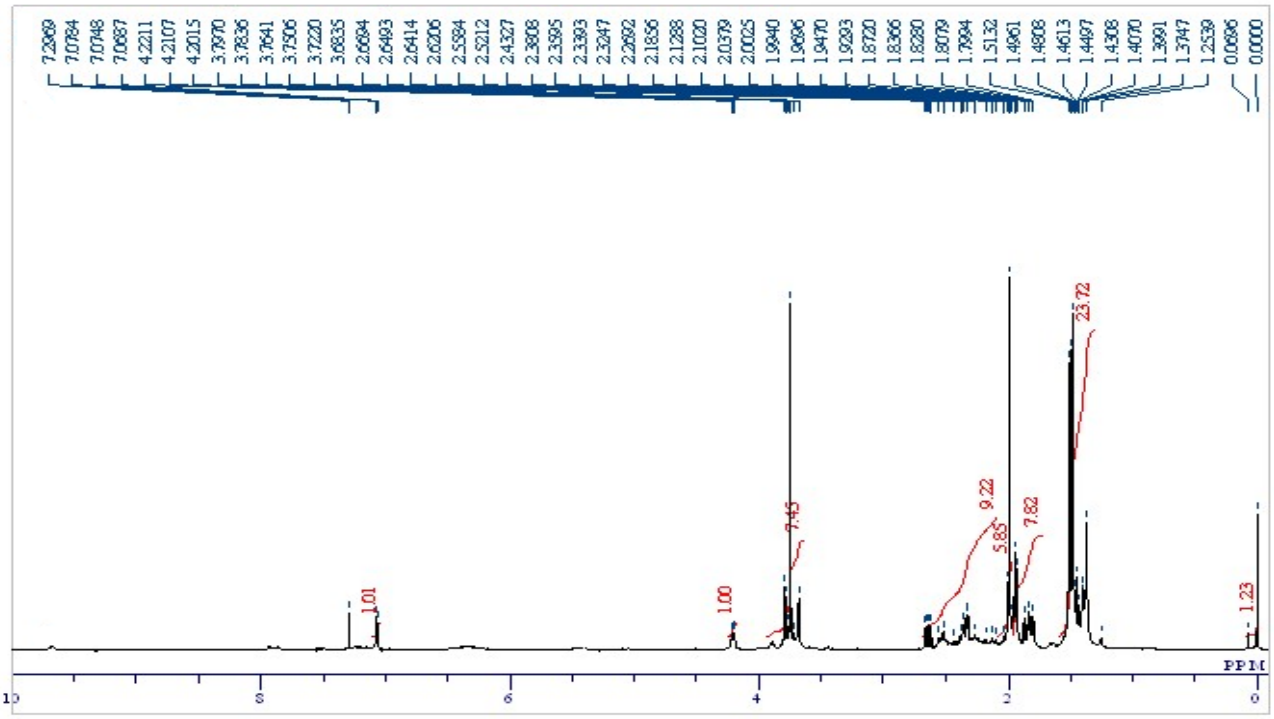
DEPT-NMR of **200** in $CDCl_3$ at 20°C



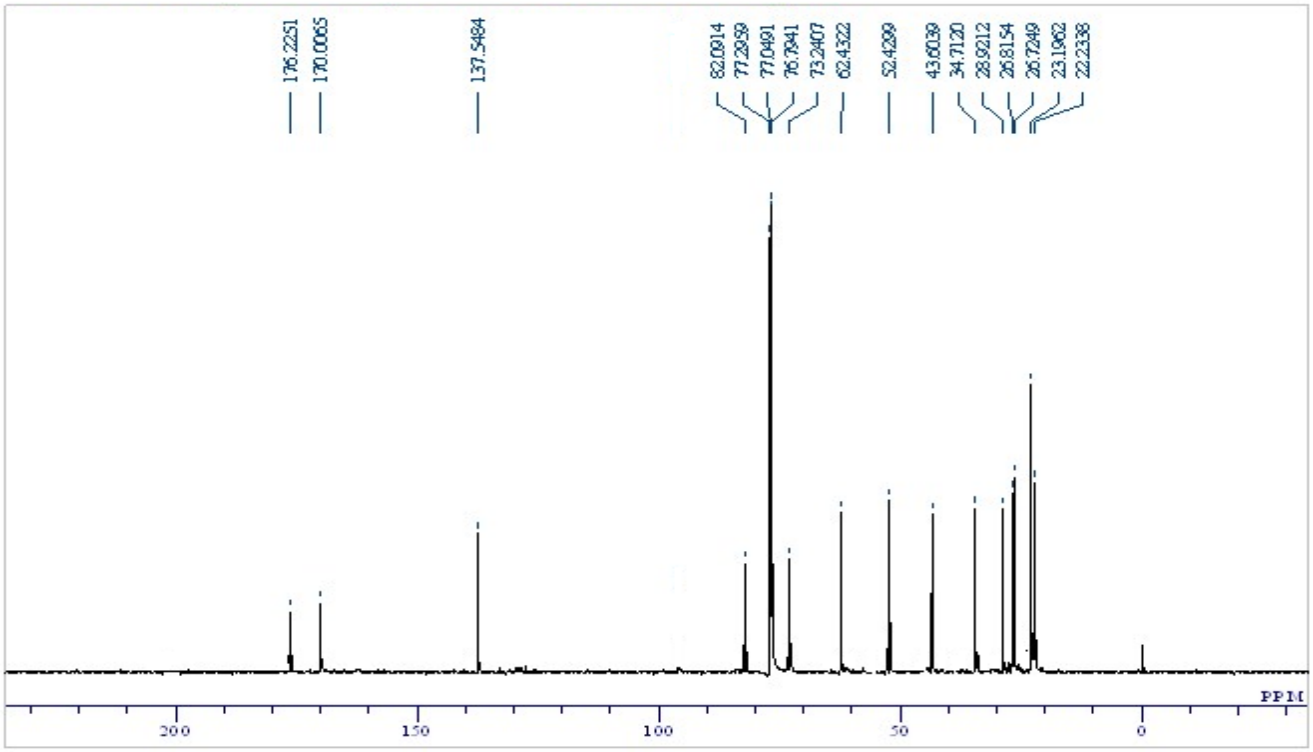
^{1}H-NMR of **202** in $CDCl_3$ at 20°C



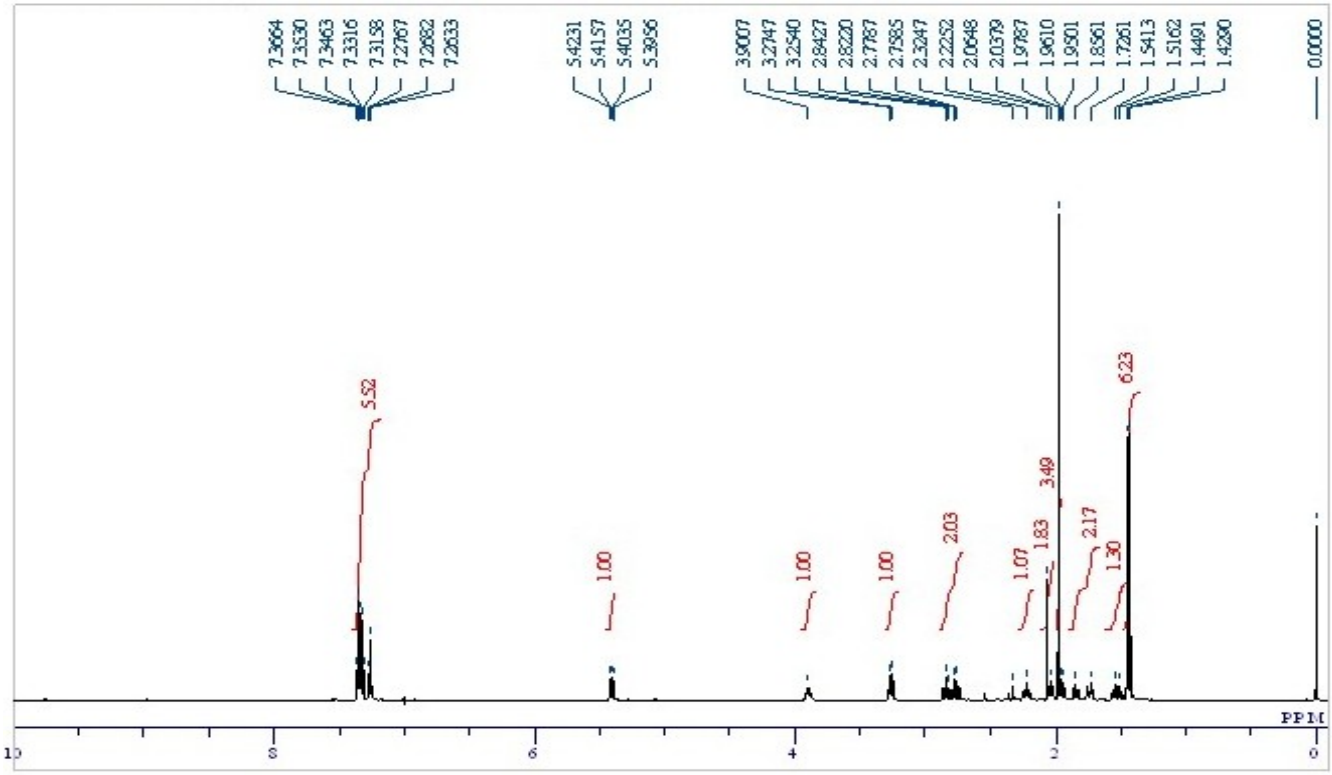
^{13}C-NMR of **202** in $CDCl_3$ at 20°C



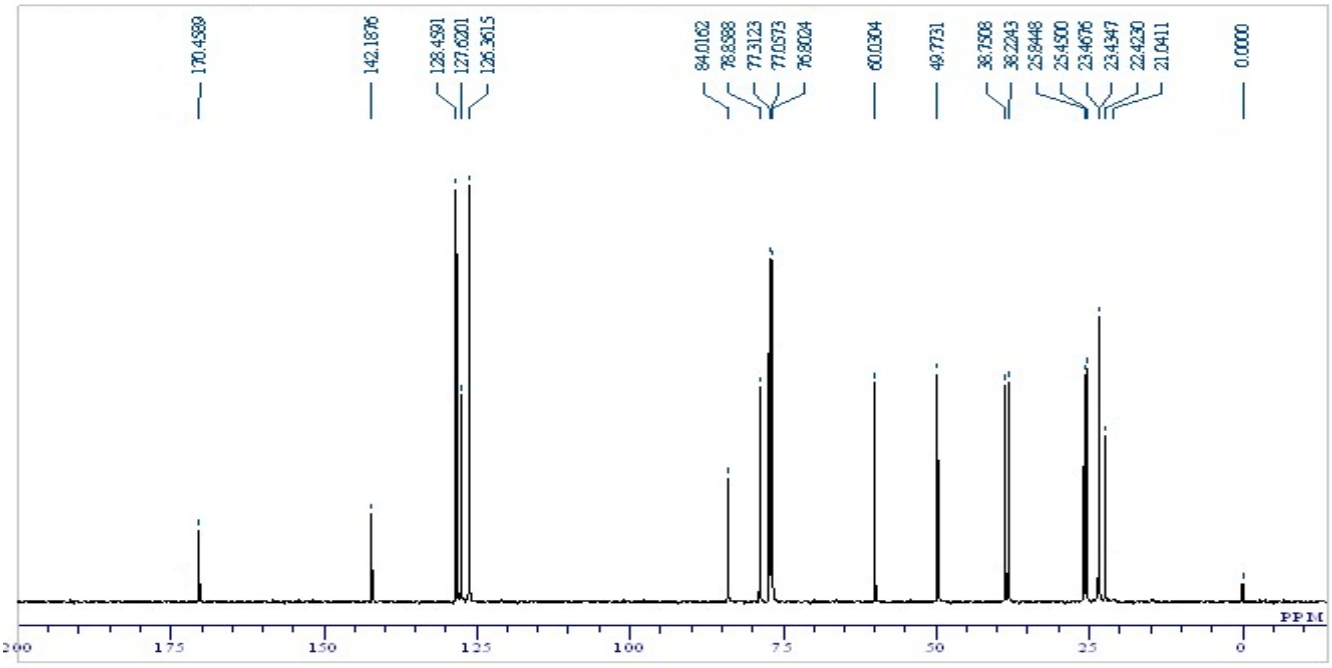
^{1}H-NMR of **203** in $CDCl_3$ at 20°C



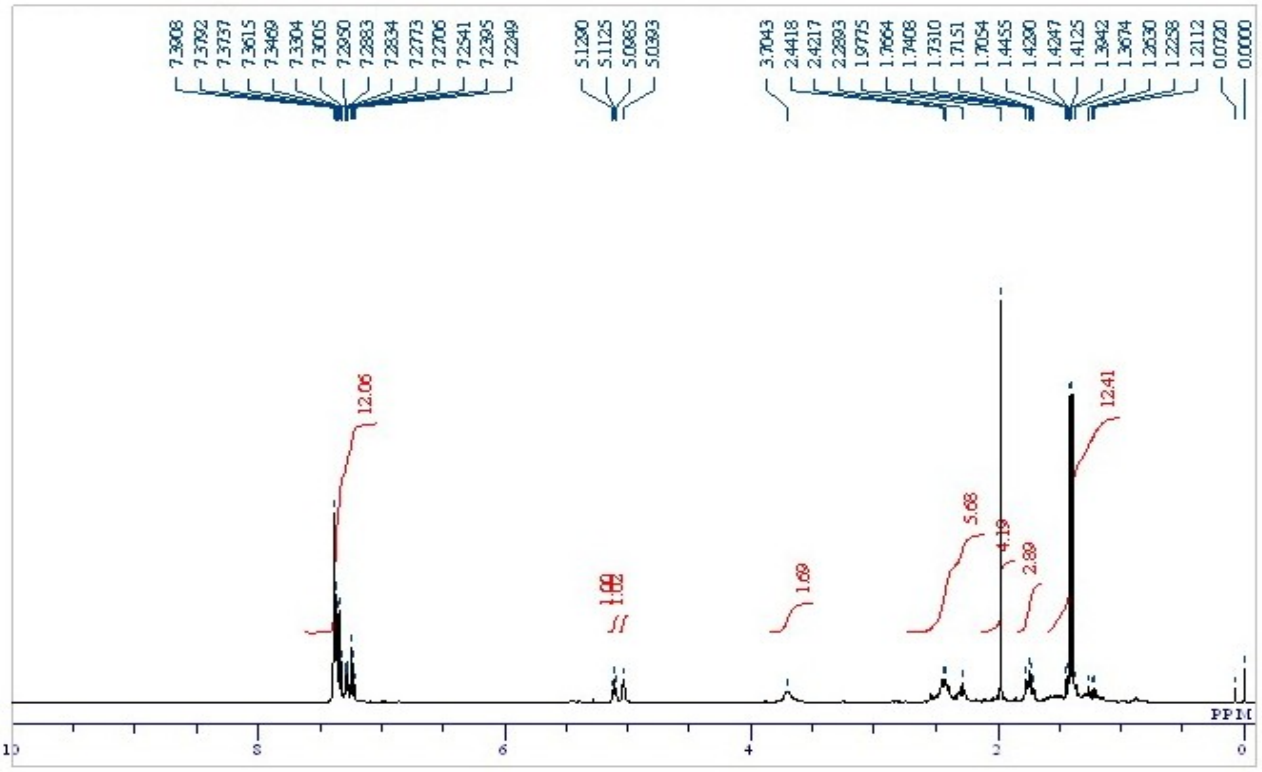
^{13}C-NMR of **203** in $CDCl_3$ at 20°C



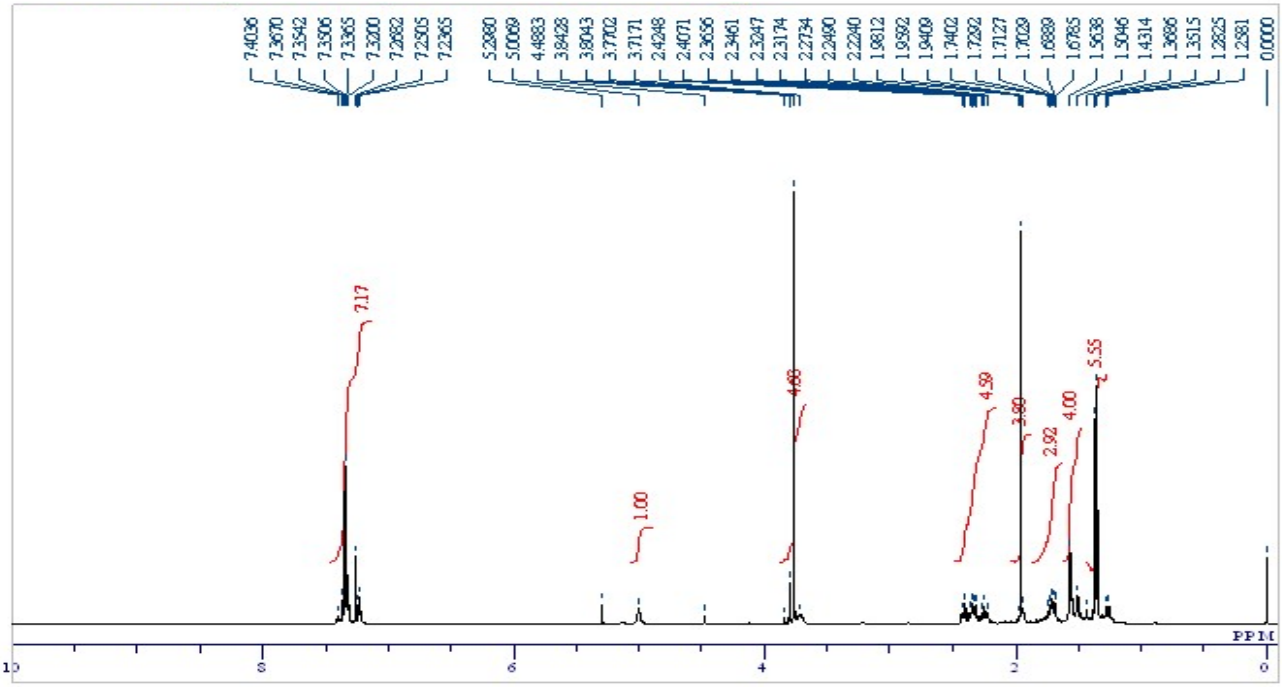
^{1}H-NMR of **201** in $CDCl_3$ at 20°C



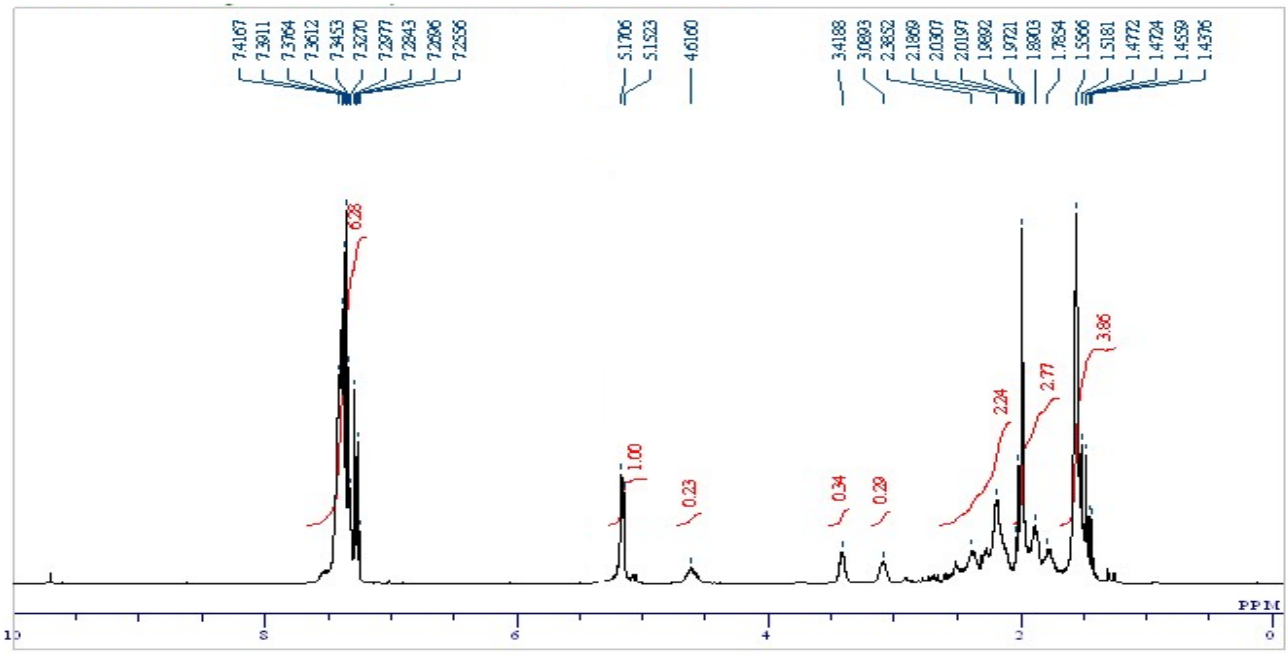
^{13}C-NMR of **201** in $CDCl_3$ at 20°C



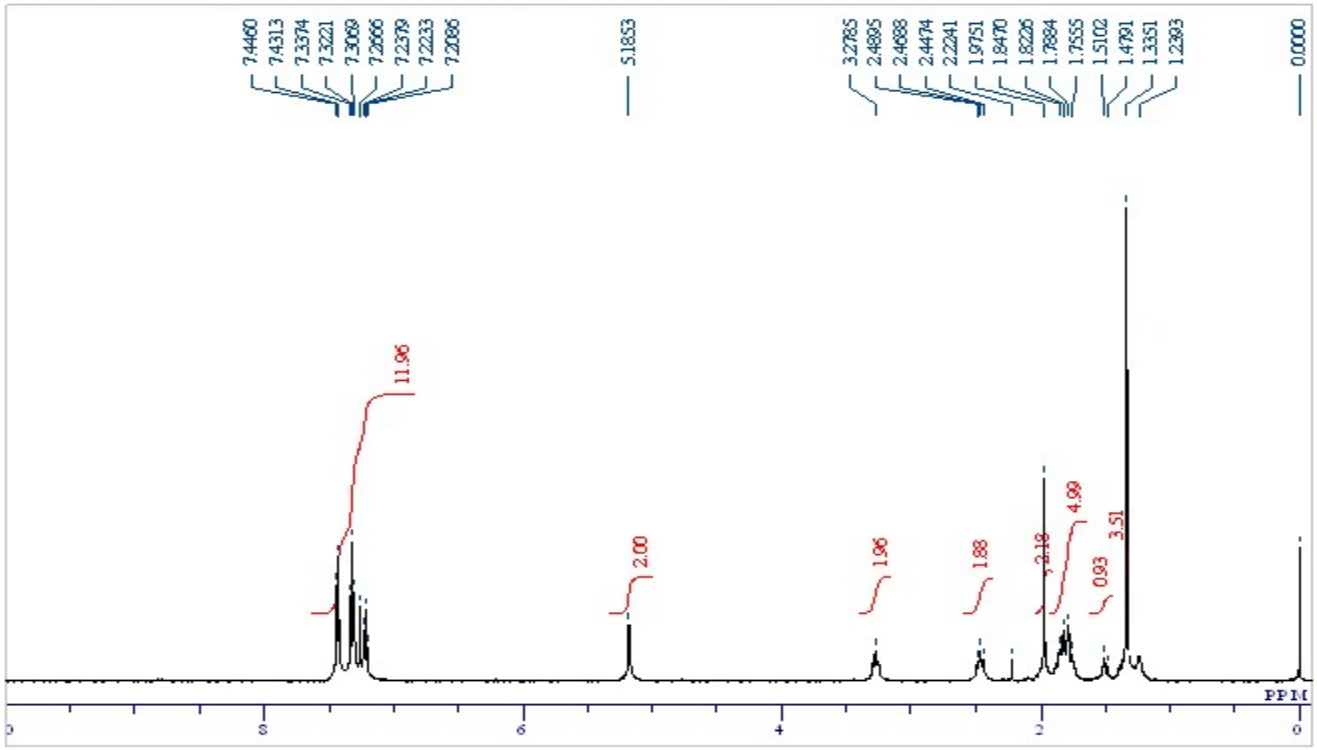
^{1}H-NMR of **206** in $CDCl_3$ at 20°C



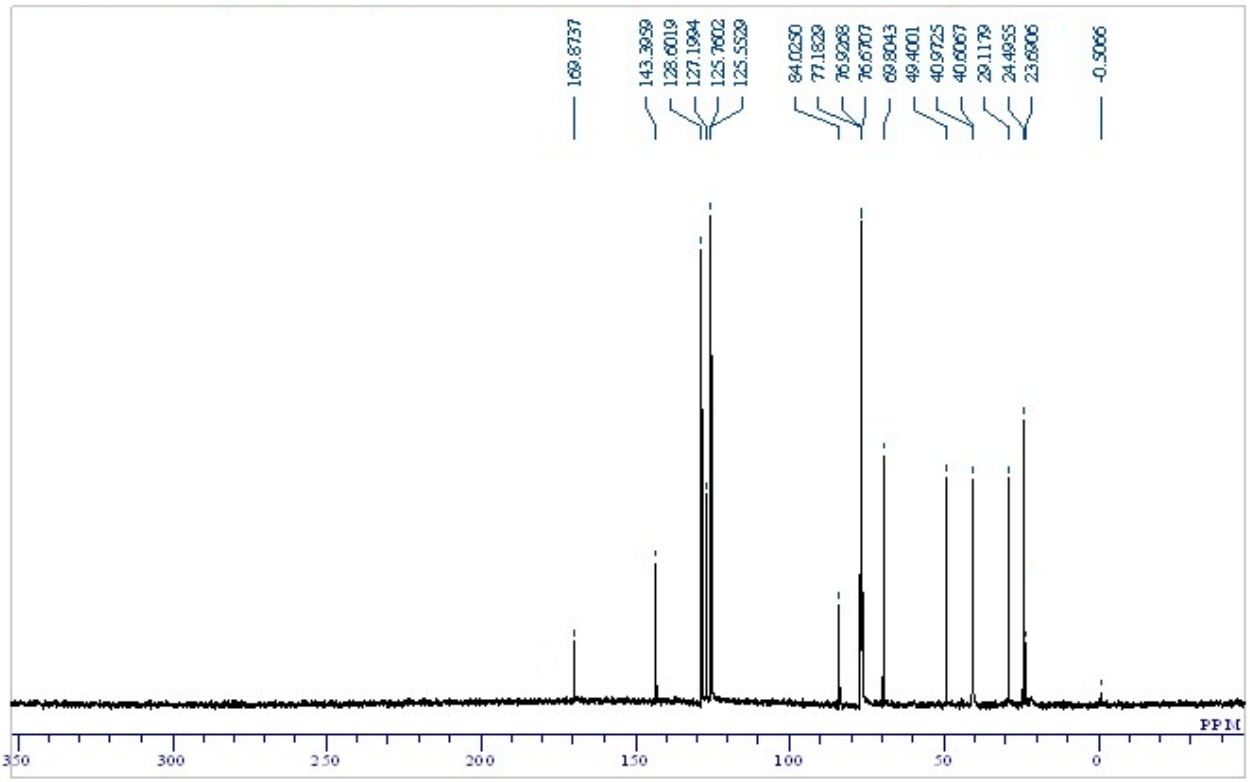
^{1}H-NMR of **205** in $CDCl_3$ at 20°C



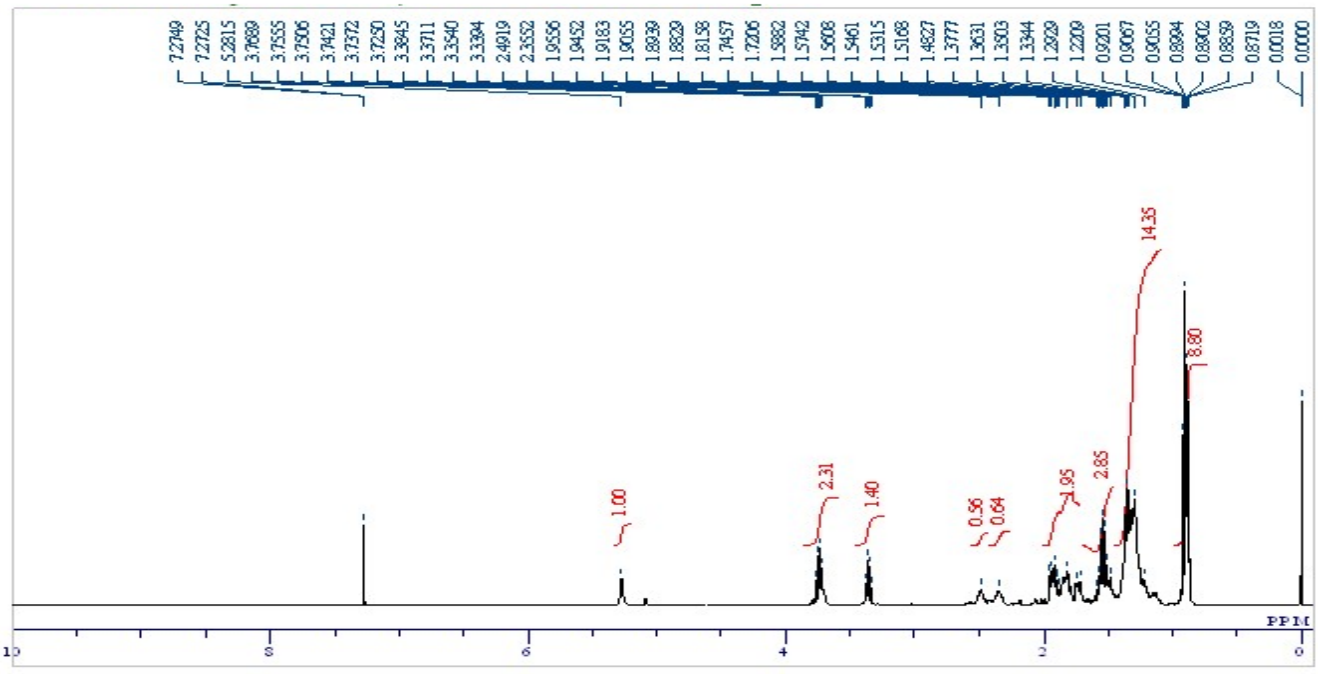
^{1}H-NMR of **207** in $CDCl_3$ at 20°C



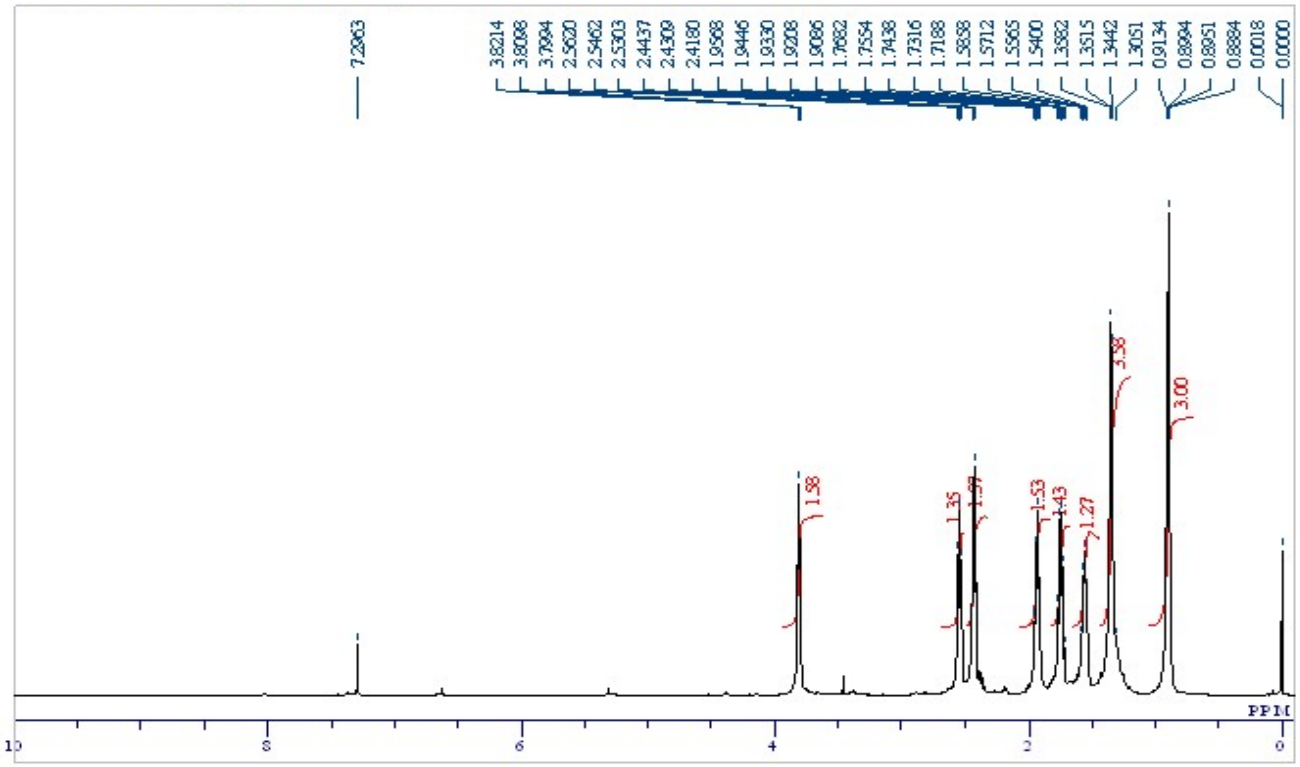
^{1}H-NMR of **208** in $CDCl_3$ at 20°C



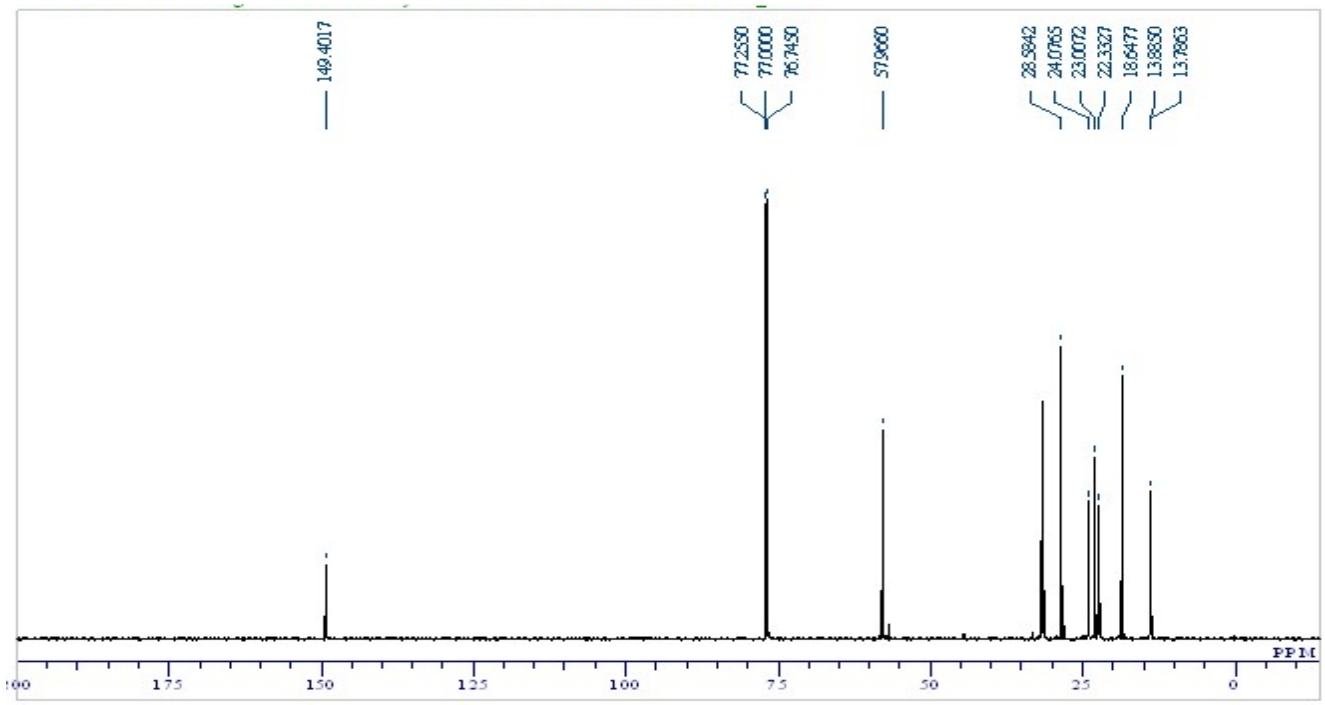
^{13}C-NMR of **208** in $CDCl_3$ at 20°C



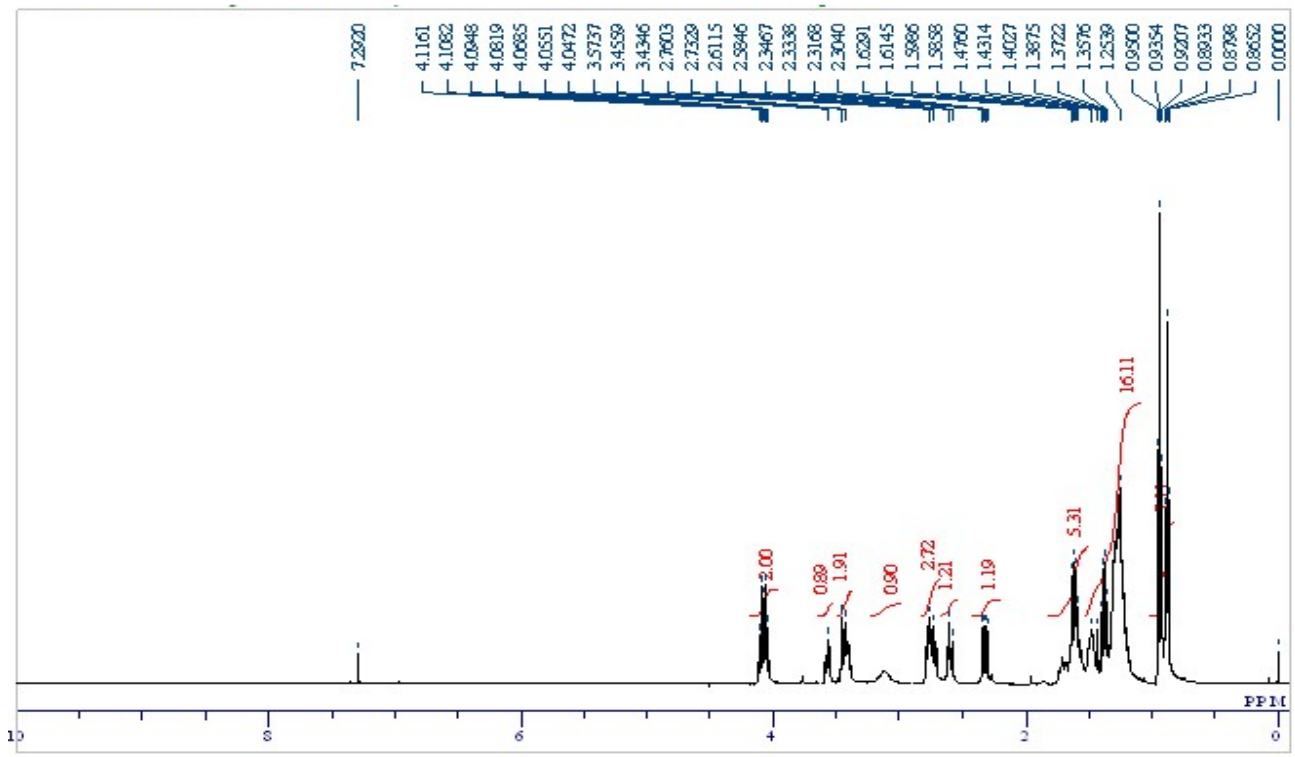
^{1}H-NMR of **258a** in $CDCl_3$ at 20°C



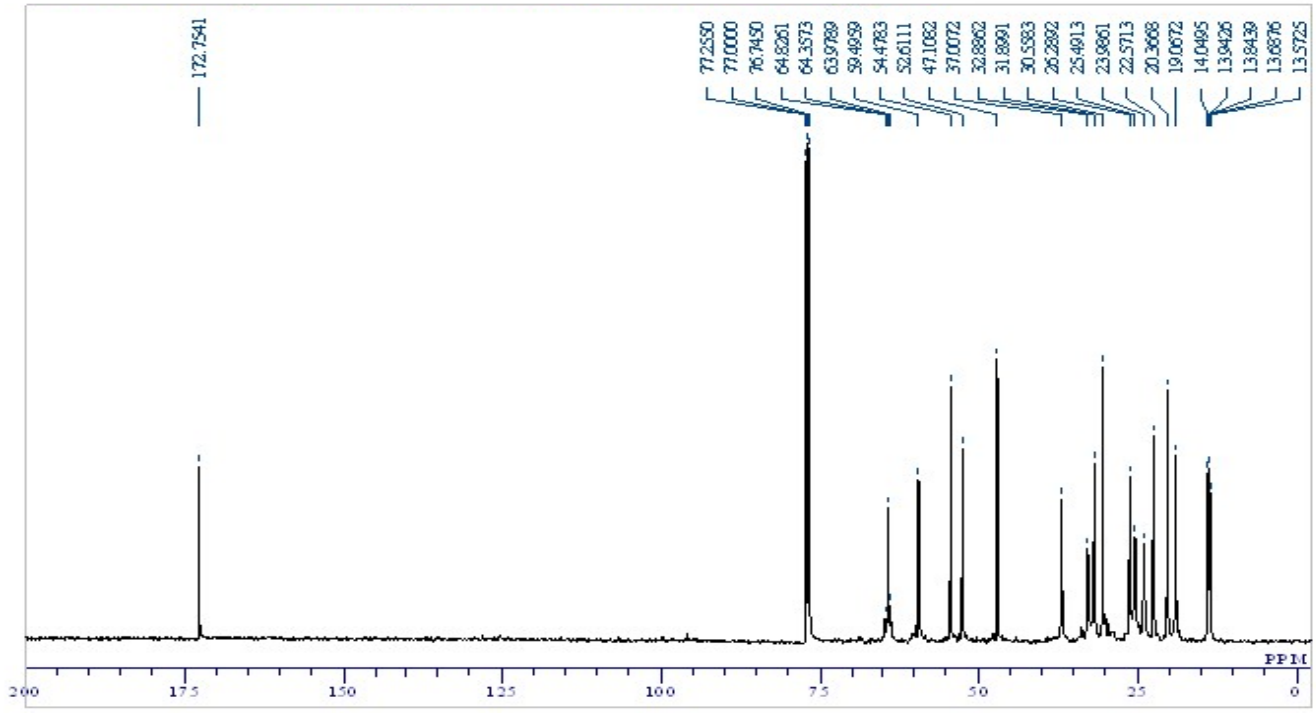
^{1}H-NMR of **264** in $CDCl_3$ at 20°C



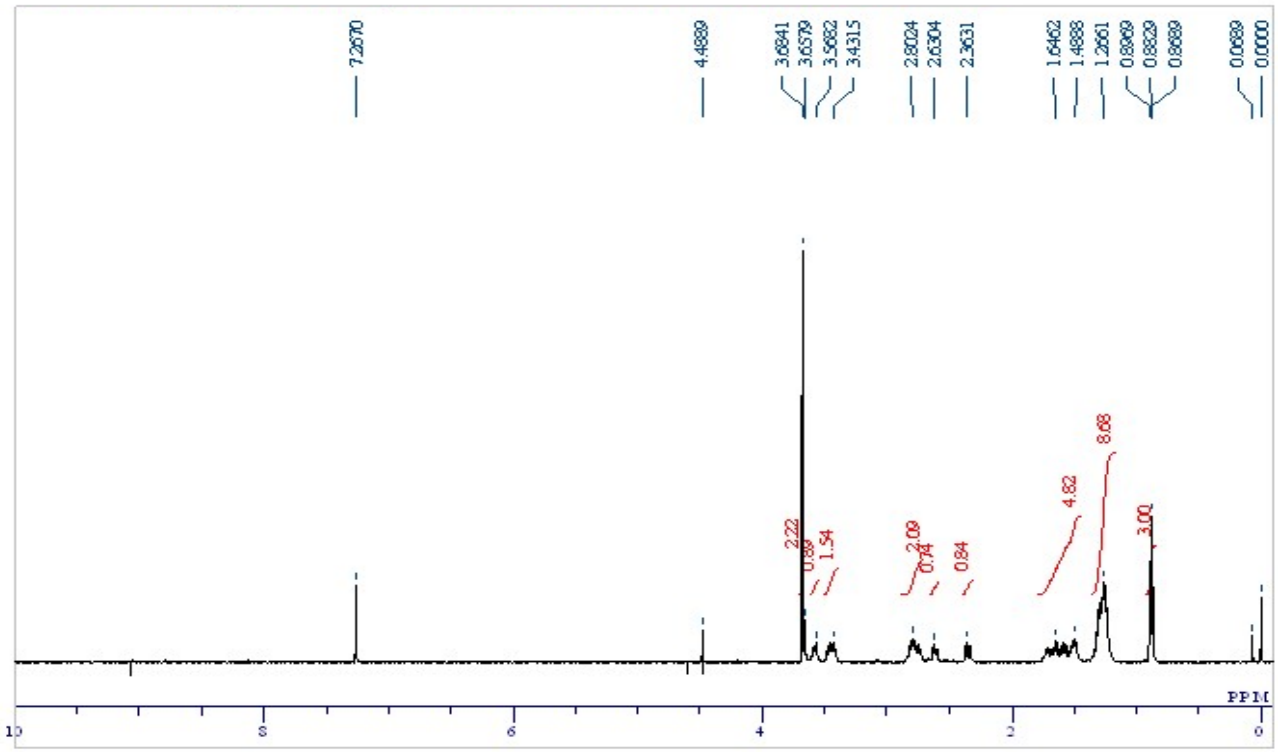
^{13}C-NMR of **264** in $CDCl_3$ at 20°C



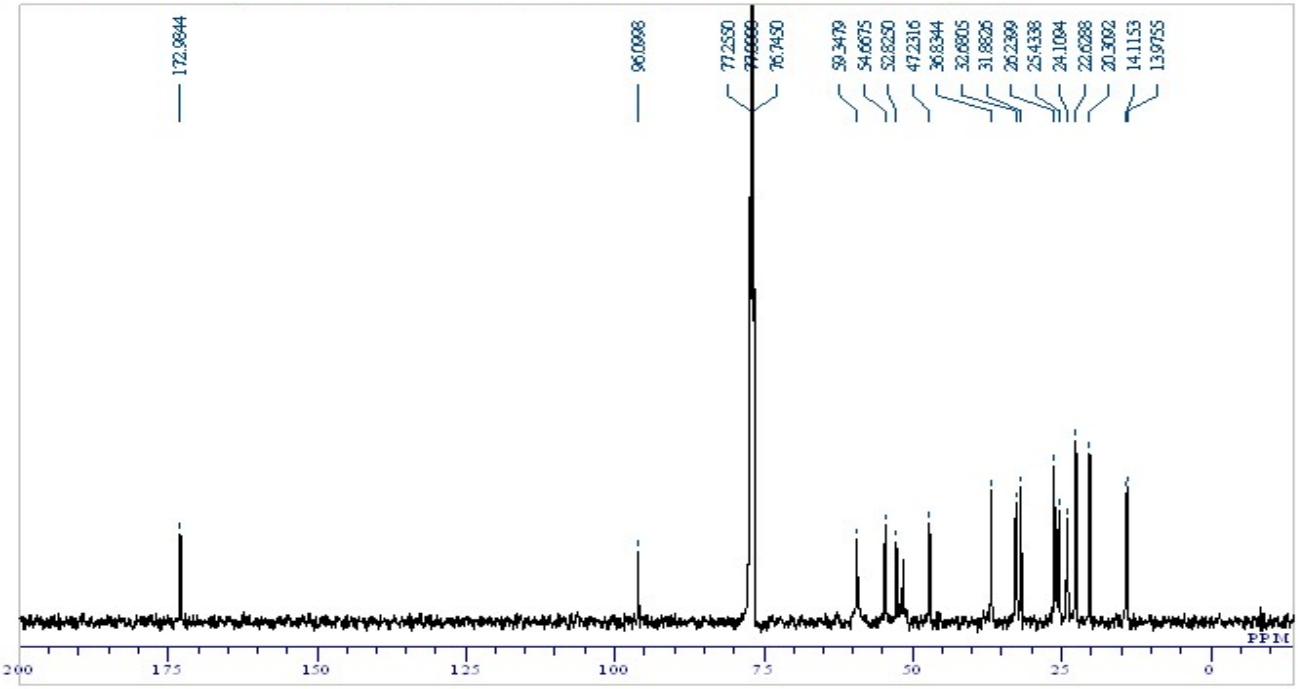
^{1}H-NMR of **260** in $CDCl_3$ at 20°C



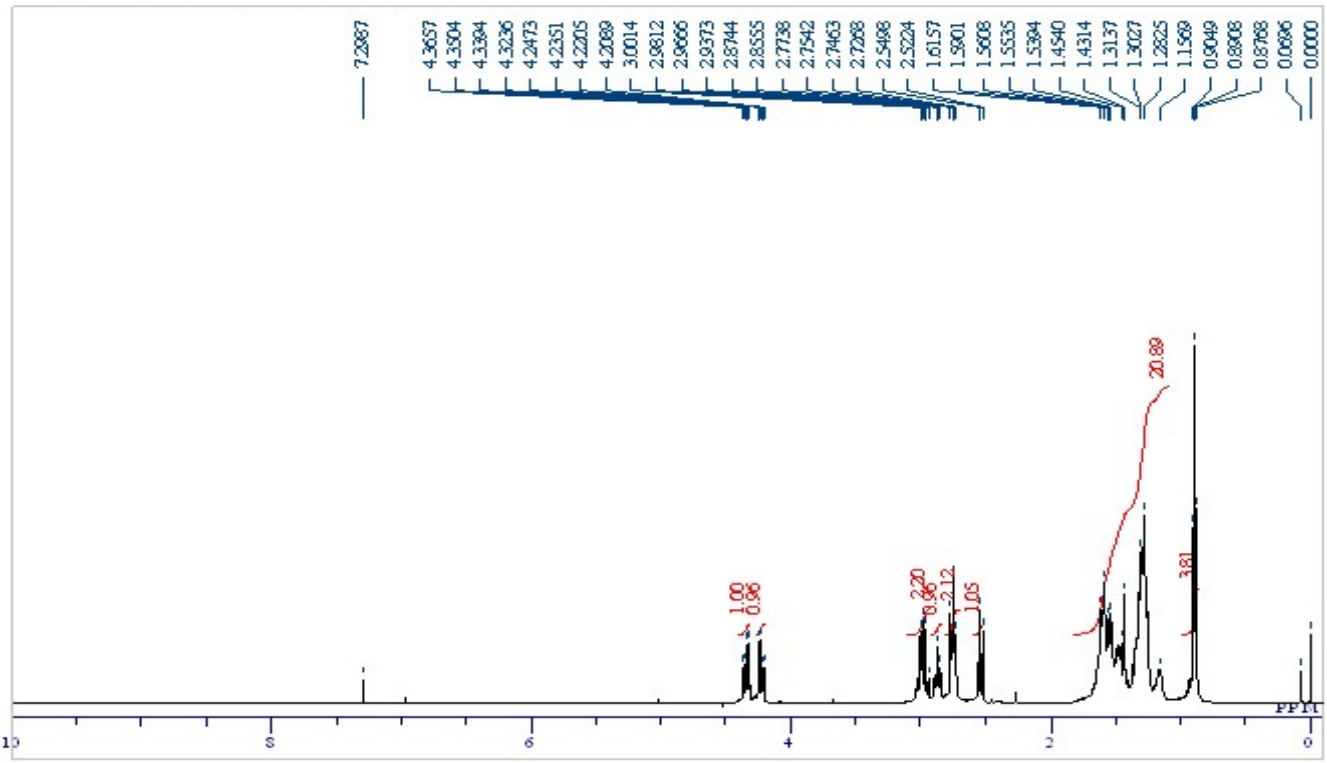
^{13}C-NMR of **260** in $CDCl_3$ at 20°C



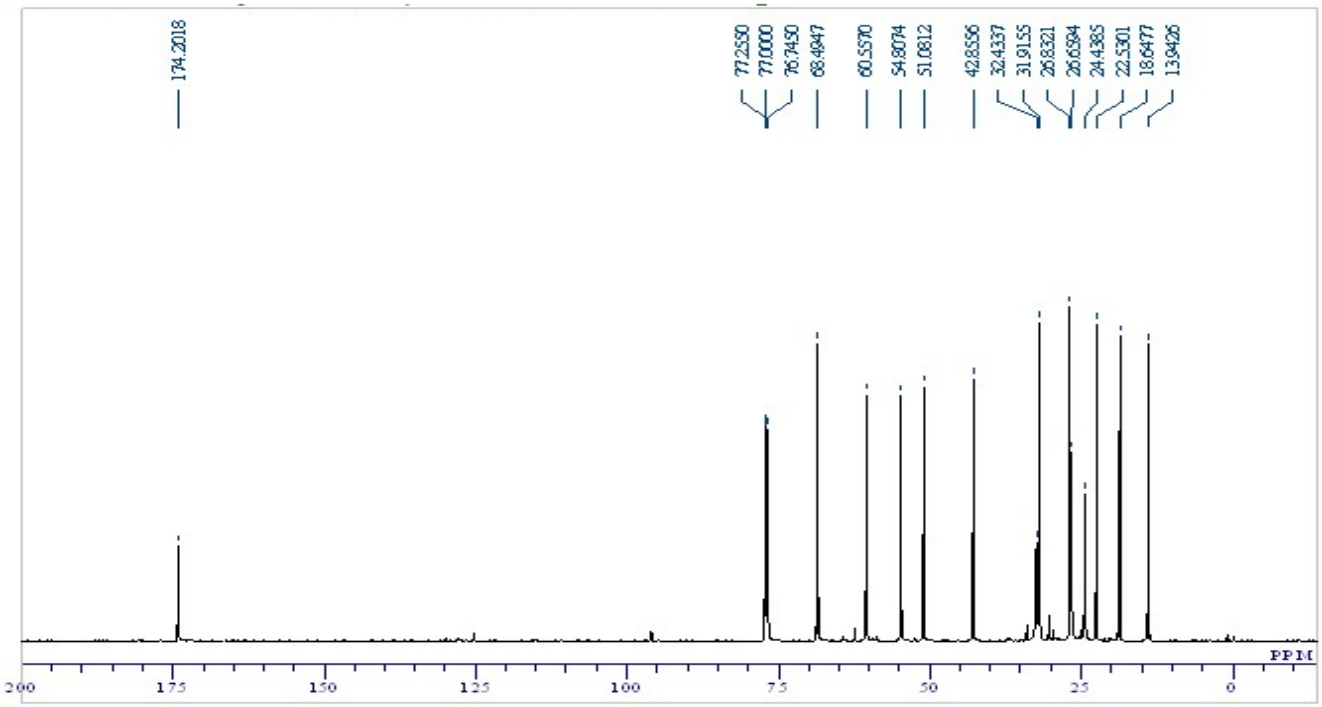
^{1}H-NMR of **261** in $CDCl_3$ at 20°C



^{13}C-NMR of **261** in $CDCl_3$ at 20°C



^{1}H-NMR of **2-epicalvine** in $CDCl_3$ at 20°C



^{13}C-NMR of **2-epicalvine** in $CDCl_3$ at 20°C

VITA

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